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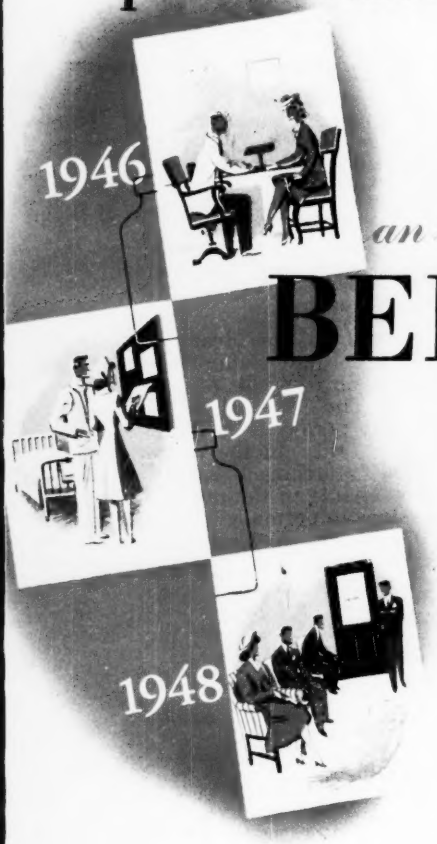

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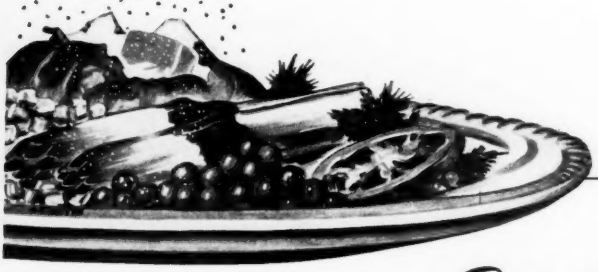

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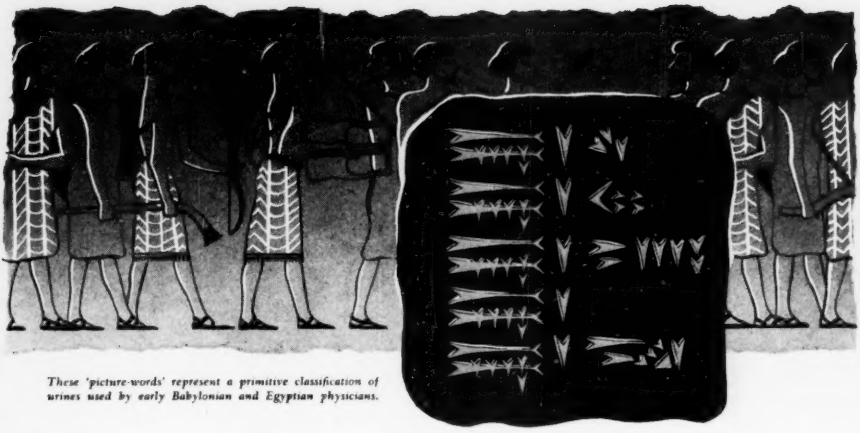

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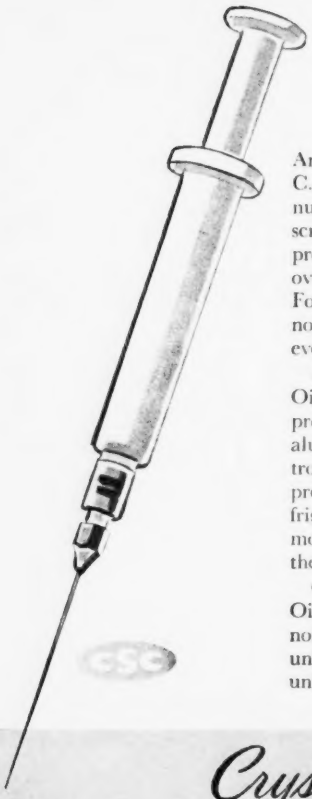

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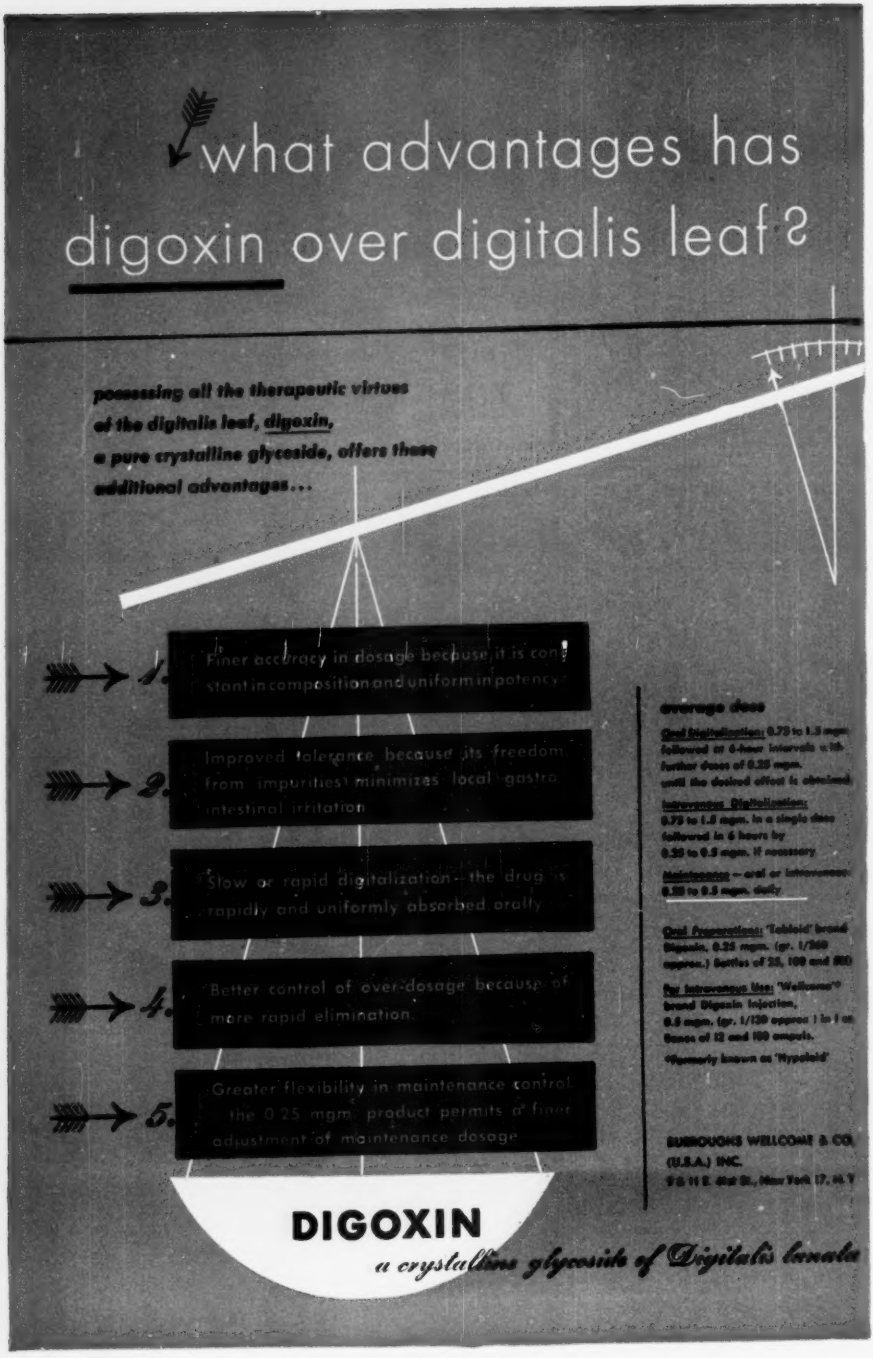
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EPIDEMIOLOGIC ASPECTS OF THYROTOXICOSIS

E. MEULENGRACHT, M.D.
COPENHAGEN, DENMARK

DURING the years 1941 to 1945 there occurred a most striking epidemic of thyrotoxicosis in Denmark. The epidemic was described and discussed by Meulengracht [1] while it was at its climax, and it has since received a detailed analysis by Kurt Iversen,[2] who has published a monograph on it. The cause of the epidemic is unexplained. As Means has so aptly expressed it to me, it remains for the time being as "just a brutal fact" which calls for an explanation.

It may perhaps be expedient, as the starting point for new investigations, to set down some epidemiologic facts regarding this temporary rise in the frequency of the disease and about the complaint itself.

EARLIER OBSERVATIONS ON THE EPIDEMIC OCCURRENCE OF THYROTOXICOSIS

In Iversen's recently published monograph there is an extensive review of the literature relating to temporary rises in the frequency of thyrotoxicosis. It appears from this that there are a number of more or less reliable observations of such temporary rises.

Thus, as early as 1890 Reynolds [3] reported that he had noted a "striking rise in the incidence of Graves's disease" in his practice during the years 1886 to 1890, and he advanced some speculations on the causes of it. A similar observation was reported by Maude in 1893.[4]

There were a number of short communications on the frequency of thyrotoxicosis in Europe in the years during and shortly after the first world war. The substance of some of them (Bérard,[5] Marañón [6] and Firgau [7]) was that a rise in the frequency of the disease had been

From the Medical Clinic B, Bispebjerg Hospital, Copenhagen.

1. Meulengracht, E.: Nord. med. (Hospitalstid.) **18**:639, 1943; Acta med. Scandinav. **121**:446, 1945.

2. Iversen, K.: Temporary Rise in the Frequency of Thyrotoxicosis in Denmark 1941-1945, Copenhagen, Rosenkilde & Bagger, 1948.

3. Reynolds, J. L.: Lancet **1**:1055, 1890.

4. Maude, A.: Lancet **2**:1003, 1893.

5. Bérard, L.: Bull. Acad. de méd., Paris **76**:428, 1916.

6. Marañón, G.: Ann. de méd. **9**:81, 1921.

7. Firgau, F.: Deutsche med. Wchnschr. **52**:511, 1926.

observed, which the authors were inclined to attribute to nervous influences due to the war ("war Basedow"). The basis of other communications (Romberg,[8] Pulay,[9] Curschmann,[10] Tallquist,[11] Klose[12] and Jacobowitz[13]) was that a fall in the frequency had been detected. This seems to have occurred particularly at places where there had been long-continued undernourishment.

In the interval between the two world wars there were a few articles on increased frequency of thyrotoxicosis, Wiesel[14] and Borak,[15] Bircher[16] and McClure[17] having reported rises in the number of cases of thyrotoxicosis. In their discussions on its causes the term "iodine Basedow" was substituted for the term "war Basedow."

A description of a temporary rise in the frequency employing the word epidemic first occurred in a paper by Plummer[18] in 1931. The communication was short and entitled "Exophthalmic goiter in Olmstead County, Minnesota." Among other things the following statement is made:

> It is probable that a wave of higher incidence followed the influenza epidemics of 1899 and 1918. The latter wave was marked by high intensity and mortality. Our data indicate a low incidence in 1923. Correlation of a number of observations led to the conclusions that the incidence of exophthalmic goiter and adenomatous goiter with hyperthyroidism rapidly increased in 1924, reached its height in 1926 and 1927, gradually diminished in 1928 and 1929, and dropped rapidly to approximately 1923 level in 1931. At the height of this wave the incidence of exophthalmic goiter in portions of the upper Mississippi Valley and Great Lakes region was three to four times that of any preceding period. This high incidence was accompanied by a marked increase in the intensity of adenomatous goiter with hyperthyroidism. Without any implication regarding etiology, I will for convenience refer to this wave of high incidence as an epidemic. There has occurred a definite drop in the intensity of adenomatous goiter with hyperthyroidism as indicated by basal metabolic rate studies. That there has been a corresponding drop in the intensity of exophthalmic goiter seems probable, but the evidence is too confused by the use of iodine in the treatment to permit as yet a definite opinion. The outstanding observations that first suggested the probability of this epidemic were too sudden a change in the number of patients having exophthalmic goiter

8. Romberg, E.: München. med. Wchnschr. **62**:673, 1915.
9. Pulay, E.: Ztschr. f. klin. Med. **88**:87, 1919.
10. Curschmann, H.: Klin. Wchnschr. **1**:1296, 1922; Acta med. Scandinav. **57**:240, 1923.
11. Tallquist, T. W.: Acta med. Scandinav. **56**:640, 1922.
12. Klose, H.: Die Chirurgie der Basedowschen Krankheit, Stuttgart, Ferdinand Enke, 1929, vol. 44.
13. Jacobowitz, H.: Ztschr. f. klin. Med. **122**:307, 1932.
14. Wiesel, J.: Med. Klin. **21**:1445, 1925.
15. Borak, J.: Wien. klin. Wchnschr. **39**:355, 1926.
16. Bircher, E.: Klin. Wchnschr. **4**:742, 1925.
17. McClure, R. D.: Ann. Surg. **85**:333, 1927; Science **82**:370, 1935.
18. Plummer, H. S.: Exophthalmic Goiter in Olmstead County, Minnesota, Tr. A. Am. Physicians **46**:171, 1931.

and adenomatous goiter coming to the Mayo Clinic from certain sections to be reasonably accounted for except by the change in incidence, a coincident change in sex ratio, a marked change in the proportions of cases of adenomatous goiter with and without hyperthyroidism, and the sharp elevation in the average basal metabolism of cases of adenomatous goiter with hyperthyroidism.

With regard to the causes of the epidemic, Plummer writes: "There is not sufficient evidence to express an opinion regarding the cause of this epidemic."

Something in the nature of an epidemic was apparently also observed by Wagner [19] at Breslau, Germany. Under the title: "Auffallende Zunahme des Morbus Basedow by Männern," he relates how the number of patients admitted to his department in 1931 suddenly rose to twice the usual figure. Among these there were a remarkable proportion of males, namely, 43 per cent against 10 per cent previously, and a striking number of elderly women with predominant cardiac symptoms. On the

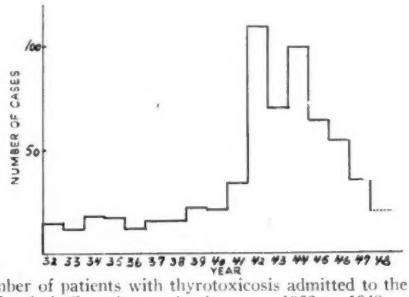

Fig. 1.—Number of patients with thyrotoxicosis admitted to the medical clinic B at Bispebjerg Hospital, Copenhagen, in the years 1932 to 1948.

subsequent course of the rise—whether it was temporary or permanent—nothing is said.

THE DANISH EPIDEMIC

The Danish epidemic began to manifest itself in 1941-1942. The medical and surgical departments were then flooded with patients with thyrotoxicosis, where, of course, such patients are admitted, but it was also noted by the general practitioners and was reflected in the neurologic and psychiatric departments. The epidemic affected the metropolis, the provincial towns and the country districts. Its magnitude can best be illustrated by a few curves. The curve given in figure 1 shows the number of patients admitted to my department, which is Medical Department B at Bispebjerg Hospital. The first part of the curve was published in 1943, but it is now brought up to date. The hospital is a municipal hospital and accepts, without selection, patients with all

19. Wagner, A.: Med. Klin. **28**:720, 1932.

descriptions of medical diseases sent by general practitioners. The material represented by the curve was critically examined, every single record being analyzed. It comprises both primary thyrotoxicosis and secondary thyrotoxicosis (toxic adenoma), but cases of the latter constitute only a small proportion of the whole. Patients for whom the diagnosis was uncertain and patients readmitted are excluded. Patients who had previously had thyrotoxicosis but had now recovered have not been included, but those with real relapses have been.

It will be seen that the rise, beginning modestly in 1941, mounted violently in 1942, while in 1943 and 1944 the number remained high. About 100 new patients were admitted each year to the department. In 1945 the number began to fall, and in 1946 and 1947 the rise died out. Corresponding rises in numbers occurred in the other medical departments in Denmark.

A curve from a single hospital department, however, ought not to be taken as representing a rising morbidity in the population. A number of fortuitous and personal factors contribute to the number of cases in a single hospital department. In order to obtain a reliable impression of the morbidity, Iversen [2] planned an investigation into the morbidity among the people of Copenhagen. His material comprised altogether 2,802 patients with thyrotoxicosis, representing all hospitalized patients with that disease in Copenhagen in the period 1938 to 1945.

Since, practically speaking, every patient in Copenhagen for whom a diagnosis of thyrotoxicosis is made is sent to a hospital and since the opportunities of being sent and admitted to hospital were unchanged during the years concerned, the number of patients in hospital represents the morbidity. The record of each individual case was examined by Dr. Iversen personally. Doubtful cases and patients readmitted to the hospital were rejected. The patients were recorded according to name and date of birth so as to ensure that their condition had been diagnosed for the first time and that no case was counted twice. Not only were the patients from medical departments recorded, but those from the surgical, neurologic and psychiatric departments were also added to the list.

The curve given in figure 2 is based on Dr. Iversen's results, and table 1 gives the number of cases compared with the number of inhabitants in Copenhagen. It is clear from the curves for the severe cases in which exophthalmos was present, the severe cases in which exophthalmos was absent and the mild cases that it is not particularly the last class which has increased in frequency. Dr. Iversen's book contains further information. The rise in frequency was greater for men than for women, and it was greater in the older age group. The symptomatology has changed to a certain degree. The rise in the number of cases of toxic nodular goiter was about twice that in the

number of cases of toxic diffuse goiter. The percentage of cases of toxic nodular goiter increased from between 11 and 12 per cent to 23 per cent of the whole material. The number of true recurrences rose parallel with the total rise in frequency; a notable percentage increase in the incidence of recurrences, however, did not appear until 1945.

Iversen's curve is the one that gives the most reliable picture of the Danish epidemic. Unfortunately, the investigation does not extend beyond 1945, so for the present only the curve obtained from the data

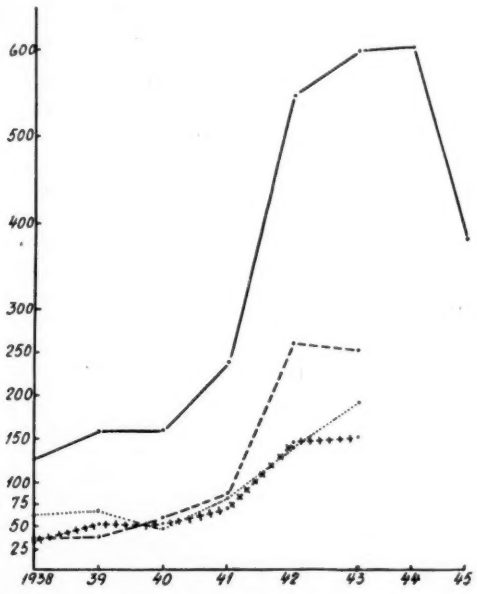

Fig. 2.—Variations in the number of the first-diagnosed cases of thyrotoxicosis in absolute figures for the entire material (——) and groups (severe cases with exophthalmos + + + +; severe cases without exophthalmos — — — —; mild cases . . . .); from Iversen, 1948.

at the Bispebjerg Hospital, given previously, can be used to represent the last stage of the epidemic. From this curve, it is sufficiently clear that the epidemic has now subsided, which state of affairs is also reported from all other medical and surgical departments in Denmark.

RISE IN THE FREQUENCY IN COUNTRIES OTHER THAN DENMARK IN THE YEARS 1941 TO 1945

From official reports and by private means, Iversen has accumulated information on the frequency of thyrotoxicosis in countries other

than Denmark in the same years as those in which the Danish epidemic occurred. It appears from the facts obtained that there was a simultaneous temporary rise in two countries, namely, Norway and France.

In Norway there was a genuine epidemic in the years 1941 to 1943. It has been described by Grelland.[20] It did not reach the same intensity

TABLE 1.—*Shift in the Morbidity Percentage of Thyrotoxicosis for the Town of Copenhagen in 1938 to 1945 (After Iversen)*

	No. of Cases	No. of Inhabitants	No. of Cases per Thousand Inhabitants
1938	129	687,625	0.19
1939	159	691,995	0.23
1940	160	700,465	0.23
1941	240	702,424	0.34
1942	546	711,224	0.77
1943	598	714,589	0.84
1944	591	724,071	0.83
1945	379	731,707	0.52

as the Danish one, since the number rose to between 100 and 200 per cent of what it had been in the preceding period, but compared with the year 1934 there was an increase of 400 to 500 per cent.

In France, but apparently confined to Paris, there was an epidemic in the years 1941 to 1944, with its peak in 1942-1943. The rise was considerable. The number of patients admitted to the public hospitals in Paris rose to three or four times what it had been in the years immediately before.

TABLE 2.—*Number of Patients with "Goitre Exophthalmique" Admitted to the Public Hospitals in Paris (Private Communication from Dr. G. Allison to Dr. Iversen)*

1938	32
1939	80
1940	90
1941	255
1942	271
1943	320
1944	102

POSSIBLE CAUSES OF THE TEMPORARY RISE IN FREQUENCY

It emerges from what has been said previously that from time to time rises and falls in the frequency of thyrotoxicosis have been observed in many different places, and sometimes (Plummer's epidemic, the Danish epidemic and the Norwegian and French epidemics) time-

20. Grelland, R.: Acta med. Scandinav. **125**:108, 1946.

limited and geographically circumscribed rises in the frequency of the disease occurred which were of such dimensions that they possessed the character of definite epidemics.

It is clear that a temporary rise in the frequency of the disease of such a degree as has been described must mean that external factors play a part in the etiology of the disease. It is recognized and generally accepted that hereditary factors also contribute to the cause. This reveals itself in the fact that thyrotoxicosis occurrs not infrequently in several members of the same family, even though they have lived apart both in time and in place. In his book, Bartels [21] examined this question thoroughly. He found that heredity manifested itself in 47 per cent of cases of thyrotoxicosis on the assumption that the occurrence in the same family, even if it is among brothers and sisters, always signifies the influence of heredity and not external causes common to them.

But although there is thus a hereditary basis for the disease, there must be other external causative factors, which follows from the outbreak in epidemic form occasionally observed.

The aforementioned authors who have described rises in frequency have naturally also dealt with possible extraneous causes, usually only superficially. The different possibilities have been more thoroughly investigated and discussed by Meulengracht, Grelland and Iversen. But no explanation has hitherto been forthcoming. I will briefly refer to the various possibilities which have so far been put forward.

Improvement in Diagnosis.—The possibility of an improvement in diagnosis has not been discussed with reference to all the small rises which have previously been observed, and this includes Plummer's epidemic. It has been kept in mind in the case of the Danish and Norwegian epidemics, because during the period concerned a sharper lookout for the disease has been maintained and there has been an extensive use of determinations of the basal metabolic rate. Meulengracht, Grelland and Iversen, however, all take exception to this explanation after a thorough examination of the local conditions. Despite the fact that attention is directed to the disease and that tests of basal metabolic rates are used in both countries just as much as ever, the increased frequency of the disease has ceased in both places and the epidemic has come to an end.

Greater Hospitalization.—The possibility of greater hospitalization has been considered by the Scandinavian authors, but it must be dismissed as an explanation. The use of the hospitals in the two countries is such that practically all patients with diagnosed thyrotoxicosis are sent there, and no change in this practice was made either before or during the war.

21. Bartels, E. D.: Heredity in Graves' Disease, Copenhagen, Ejnar Munksgaards Forlag, 1941.

Iodine Treatment and Iodine Salts.—As mentioned before, some of the earlier observed rises in frequency, although transient, were attributed to iodine medication in the form of iodine salts. Plummer also mentioned the prophylactic introduction of iodine salts as a possible cause of the epidemic, but he apparently did not attach any significance to it himself. Now "iodine Basedow" is in itself an extremely problematic phenomenon whose existence is categorically denied by the majority, while in Denmark and apparently also in Norway it is unknown. As far as the Danish epidemic is concerned, the question has been fully dealt with, due regard having been paid to local conditions by Meulengracht at the commencement of the epidemic and later by Iversen. They both reject the possibility of this explanation.

Climatic Conditions.—As various experimental investigations have been made which show that exposure to cold can induce slight epithelial hyperplasia and increased vascularization of the thyroid gland in experimental animals and since Sällström [22] has demonstrated that thyrotoxicosis is commoner in the relatively colder eastern part of Sweden than in the warmer western region, Meulengracht has briefly pointed out, apropos of the Danish epidemic, that extraordinarily cold winters were experienced in Denmark in precisely the years 1940 to 1942. Iversen has enlarged on this and has extracted the information from the annual meteorologic reports that in the year which preceded Plummer's epidemic and in the year of its appearance there were also severe winters in Minnesota, where the epidemic occurred. It is difficult to prove or disprove that such climatic factors play a part, but there seems to be no strong probability in favor of it. Moreover, the severe winters of 1940 to 1942 were common to all European countries and not limited to Denmark.

Nervous Influences.—As was to be expected, this possible explanation has been the most dominant in the discussion. It was advanced by the aforementioned early observers of the rise in frequency, and during the first world war, as previously intimated, the condition was designated "war Basedow." Plummer dissociates himself from such an explanation. Meulengracht and Iversen take up a similar attitude regarding the Danish epidemic, while Grelland is unwilling to dismiss it entirely in the case of the Norwegian epidemic. It can perhaps be taken as generally recognized that nervous influences in themselves cannot be the cause of thyrotoxicosis. However, there are some authors who contend that they can in some measure hasten the clinical arrival of the symptoms, while, on the other hand, there are others who would attribute no effect at all to neurotic influences and psychic trauma. The

22. Sällström, T.: Vorkommen und Verbreitung der Thyreotoxicose in Schweden, Disputats, Stockholm, 1935, p. 206.

nonacceptance of nervous influence as the explanation of the Danish epidemic is due partly to this general view but also to irreconcilable facts. The epidemic in 1941-1942 began at a time when the country was occupied by the Germans but when the occupation still had the character of a "peaceful occupation," the mental strain and psychic shock not being so severe as in the years 1944 and 1945, with the then established acts of sabotage and terror. Then the neurotic effects of the world war were fairly universal and embraced at least the whole of Europe, while the epidemics of thryotoxicosis (the Danish and Norwegian epidemics and the one in Paris) were local events. No reports of a corresponding rise came from other places. On the contrary, according to Iversen's book, many places reported less frequent occurrences of thyrotoxicosis. Moreover, the majority of these countries were decidedly more severely hit by the events of the war, while Denmark was never a direct theater of hostilities.

Nonspecific Infections.—The problem of the possibility of the different infectious diseases producing thyrotoxicosis has been discussed in one place or another for years without any conclusion having been arrived at. Iversen investigated this question with respect to the Danish epidemic but was unable to establish any connection with catarrhal infections, tonsillitis, rheumatic fever or any other known infectious diseases. Grelland [20] reported the same finding.

Nutritional Factors.—It is known that nutritional factors have a certain effect on the development of thyrotoxicosis. Thus there is evidence to show that starvation depresses the metabolism and that general starvation diminishes the frequency of thyrotoxicosis in the population—in short, it has an inhibiting action (Tallquist,[11] Curschmann,[10] Brull,[23] Bastenie,[24] Schweitzer [25]). The question of nutritional factors has been thoroughly studied for the Danish epidemic by Iversen. He analyzed the official reports on the Danish diet during the war and showed that a certain reduction in the consumption of fats occurred which was due to the complete cessation of the production of margarine in 1941 because of the nonimportation of vegetable oils, including soya bean oil and other soya bean products. As soya contains a certain quantity of antithyroid substances, Eggert Møller [26] has tentatively put forward the view that the Danish epidemic of thyrotoxicosis might be due to deprivation of the antithyroid bodies in soya bean, an idea which has been followed up by Iversen. After a full examination of

23. Brull, L., and others: Les états de carence en Belgique pendant l'occupation allemande 1940-1944, ed. soledi, Paris, Librairie scientifique, Hermann & Cie, 1945.

24. Bastenie, P. A.; Macrae, T. F.; Smart, G. A., and Yudkin, S.: Brit. M. J. **2**:351, 1945.

25. Schweitzer, P. M. J.: Acta med. Scandinav. **119**:306, 1944.

26. Møller, E.: Ugesk. f. læger **107**:676, 1945.

the facts, however, Iversen can find no evidence to support the view that a diminished content of antithyroid bodies in the Danish people's diet was responsible for the epidemic, and he leaves the matter open. In my opinion there are even strong arguments against it. For instance, the epidemic began to decline a considerable time before the importation began to get under way again, which in point of fact even now is only on a small scale. Then again, the epidemic appeared in Denmark and Norway alone and not in Sweden, where the importation of soya bean was in like manner interrupted; and the same can be said of other countries.

CAN A SPECIFIC INFECTIVE AGENT BE THE CAUSE OF THE TEMPORARY RISE IN THE FREQUENCY OF THYROTOXICOSIS?

When one has experienced the temporary rise in frequency of the disease in Denmark at first hand, it is almost impossible to resist the impression that the increased incidence resembles an epidemic of an infectious nature. Two diseases simultaneously predominated in the medical departments of Bispebjerg Hospital—a subacute malignant form of hepatitis which all agreed to regard as a specific infectious disease (virus infection) and a form of thyrotoxicosis which nobody was willing to accept as such. In the manner of their occurrence and in their epidemic curves there was something remarkably similar.

Although for many reasons the mind recoils at the idea of thyrotoxicosis as a specific infectious disease and possibly a virus disease, it may be worth while looking a little more closely into the question and pointing out that it has certain characteristics which are in favor of an infectious origin and might support such a theory.

The different epidemics have been distinctly localized geographically. Plummer's epidemic was localized in the Upper Mississippi Valley and the Great Lakes region, Wagner's epidemic seems to have been in Breslau and the surrounding district, while in Scandinavia it was in Denmark and Norway and in France it was in Paris.

Sex Distribution.—Then there appears to be a decided shift in the sex distribution in the different epidemics. Wagner drew attention to an unusual distribution in the cases of thyrotoxicosis described by him, the number of male patients rising from the usual 10 per cent to 43 per cent. Plummer wrote that in his epidemic there was "a coincident change in the sex ratio." In the case of the Danish epidemic, Schmith and Krarup [27] found, on comparing the incidence and symptomatology in the different periods, that there had been an increase in the number of male patients during the war, that is, during the epidemic.

27. Schmith, K., and Krarup, N. B.: Nord. med. (Hospitalstid.) **18**:648, 1943.

Ehlertsen and Lebel[28] came to the same conclusion when the years 1942 to 1944 were compared with the years 1934 to 1941. Iversen found that "the rise in thyrotoxicosis among the men in Copenhagen has been greater than for the women"; in group 1 (cases during 1938 to 1940) the ratio of men to women was 1:8.0, and in group 2 (cases during 1942 and 1943) the ratio was 1:6.5. The shift was greatest in the age group 55 to 69 years (1:4.03). In the Norwegian epidemic Grelland found a greater proportion of men in the period 1940 to 1944, that is, during the epidemic, than in the period 1934 to 1939, namely, 13.6 and 10.3 per cent respectively. There is no information about sex distribution in the Paris epidemic.

Age Distribution.—An alteration in age distribution was indicated by Wagner, who stated that the feature of the rise which he observed was that many of the patients were elderly women with preponderant cardiac symptoms. As regards the Danish epidemic, the question was investigated by Schmith and Krarup,[27] Ehlertsen and Lebel[28] and Poulsen,[29] who found an increase in the number of elderly patients. Schmith and Krarup obtained an average age for the 1942 patients of 45.1 years, against 38.8 years for the preceding ten years. Iversen also found that there was a distinct shift in the direction of the older age classes. The ages were from 42 to 86 years in 1942 to 1943 inclusive, against 39 to 55 years in 1938 to 1940 inclusive, an age difference which is statistically significant. In the Norwegian epidemic Grelland found the same displacement toward the older age classes, with a mean age of 45.2 years against 40.2 in the preceding period. There is no information of this kind about the Paris epidemic.

Change in Symptomatology and Character.—This also seems to have occurred during the epidemics. The relative number of severe cases in Wagner's epidemic seems to have been larger than that elsewhere. The symptomatology and the course of the disease in the Danish epidemic have been worked out by Schmith and Krarup, Ehlertsen and Lebel, Poulsen and Iversen and compared with the symptomatology in previous periods. Schmith and Krarup found no pronounced difference except that the occurrence of exophthalmos was rarer in the epidemic. The other authors discovered distinct differences. Thus, Ehlertsen and Lebel found more oligosymptomatic patients than before, especially among the older age groups. Poulsen found that goiter was less frequent than formerly and likewise tachycardia. Iversen has made a thorough analysis of the symptomatology in the cases which occurred in the years before the rise in frequency. He too found that thyrotoxicosis during the epidemic appeared in a more oligosymptomatic

28. Ehlertsen, C. F., and Lebel, H.: Nord. med. **26**:1082, 1945.
29. Poulsen, E.: Ugesk. f. læger **107**:923, 1945.

form than previously; pronounced enlargement of the thyroid, exophthalmos and tachycardia appeared less frequently, while values for the metabolic rate were somewhat higher.

Seasonal Variation.—There are a number of investigations, mainly from Germany, on the seasonal incidence of the disease, and despite the difficulties bound up with deciding when the disease in any individual case began, they give a fairly clear impression of the conditions. Rusznyák [30] found a higher incidence in the spring and in September, Breitner [31] in the spring and early summer and Hirsch [32] in May to August. These authors recorded the cases according to the date of admission of the patient to the hospital. Oehme and Paal [33] found an increased incidence from January to May, but their cases came from an outpatient clinic. Jacobowitz,[13] on the other hand, recorded the cases

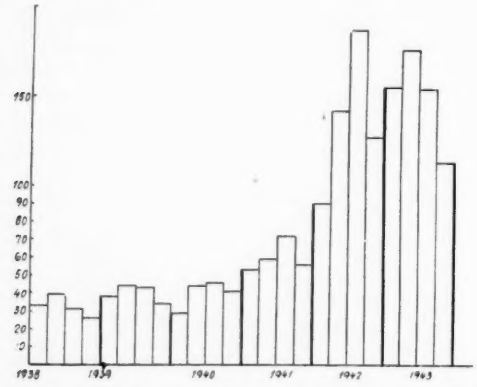

Fig. 3.—Quarterly distribution of thyrotoxicotic patients hospitalized in Copenhagen in 1938 to 1943 (Iversen, 1948).

after the commencement of the disease and found the maximum occurrence in May and the minimum occurrence in June to August. Iversen recorded the whole of his extensive material according to the month of admission. His results, which are of great interest, are represented in figures 3 and 4. It will be seen that there is a typical seasonal variation which repeats itself year after year and during the epidemic itself, with maximum occurrence in summer and minimum occurrence in winter.

30. Rusznyák, S.: Wien. Arch. f. inn. Med. **3**:379, 1922.

31. Breitner, B.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **35**:636, 1922; Münchener. med. Wchnschr. **79**:513, 1932.

32. Hirsch, D.: Deutsches Arch. f. klin. Med. **168**:331, 1930.

33. Oehme, C., and Paal, H.: Med. Klin. **26**:454, 1930.

Extent, Rise and Form of the Epidemics.—The extent, rise and form in the different epidemics seem to have been somewhat of the same dimensions. The duration was four to six years (Plummer's epidemic, 1924 to 1931; the Danish epidemic, 1942 to 1947; the Norwegian epidemic, 1941 to 1944; the Paris epidemic, 1941 to 1944). The rise was 300 to 500 per cent compared with the preceding period (Plummer's epidemic, "three to four times that of any preceding period"; the Danish epidemic, 300 to 400 per cent; the Norwegian epidemic, a little more difficult to estimate but perhaps roughly 100 to 200 per cent; the Paris epidemic, 300 to 400 per cent). The form, so far as can be judged, seems to have been fairly similar and of the same type as that in Iversen's curve for the Danish epidemic, that is, fairly symmetric and only slightly pointed.

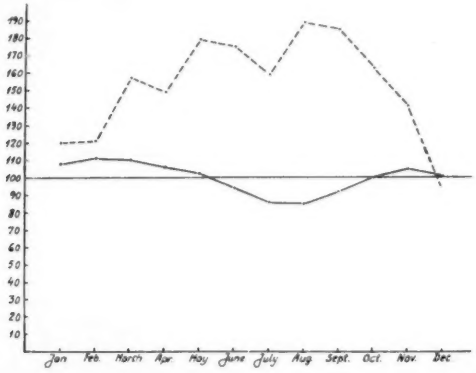

Fig. 4.—Seasonal variation in the number of thyrotoxicotic patients hospitalized in the period of 1938 to 1943 (— — — — —) compared to the relative number of patients admitted to Copenhagen city hospitals in the same period (Iversen, 1948).

Relation to Epidemics of Other Diseases.—The general epidemic position in Denmark in the period concerned was recorded in the Medical Report for the Kingdom of Denmark in 1945, published by the National Health Service of Denmark in Copenhagen in 1947. From this it appears that in the years 1940 to 1945 there was a rise in the epidemic morbidity of the notifiable acute diseases of 20 to 30 per cent. The rise was due in the main to the fact that epidemic cerebrospinal meningitis, mumps, angina and tonsillitis, acute infectious gastroenteritis, infectious hepatitis and venereal diseases increased greatly in frequency. The rises set in during the years 1940 and 1941. In the latter part of the period there were small seasonal epidemics of poliomyelitis. No rise in the frequency of influenza occurred and no increase

in epidemic encephalitis. The rise in epidemic hepatitis was particularly sharp. Beginning in 1940, it extended over the years 1940 to 1946 and comprised the ordinary acute cases. But in its wake a remarkable epidemic of malignant hepatitis with subacute atrophy of the liver broke out. This epidemic, which was described by Bjørneboe and Brøchner-Mortensen,[34] Jersild[35] and Alsted,[36] spread itself over the years 1942 to 1946. The disease, which was extremely serious and had a mortality rate of 60 to 70 per cent, attacked elderly women almost exclusively. Whether it was connected with an extension of the ordinary hepatitis or with a special virus has not been stated. No connection has been proved to exist between any of the diseases named and the cases of thyrotoxicosis.

No non-notifiable acute diseases occurred with specially noteworthy frequency during the years concerned, particularly in 1940 and 1941. There seems, however, to have been a slight increase in cases of acute polyradiculitis (radiculomeningomyelitis). No rise in occupational, industrial or nutritional toxic effects was observed.

The state meteorologist, Helge Petersen,[37] has constructed by a mathematical process the theoretic epidemic curves, using various imaginary "mechanisms" for the spread of an infective agent. These curves were in surprisingly close agreement with the actual ones. This opens up the possibility of arriving at a conclusion as to the mode of infection by a mathematical analysis of the epidemic curves of a given infectious disease. I have asked Petersen whether, on the assumption that an infectious disease is being dealt with, it would be possible to undertake such a calculation with the scanty material available on epidemics of thyrotoxicosis. He has kindly attempted to do so. The basis of the calculation was the seasonal variations as they have been recorded by Iversen (see figure 3). Petersen writes:

I have carried out a calculation based on Fig. 11, p. 67, of Kurt Iversen's thesis for the years 1941, 1942 and 1943. The result is that the "tops" of the three curves are 0.12, 0.11 and 0.11 respectively. I have proceeded, in making the calculation, in such a manner that I have only made use of the true seasonal variation, that is to say, I have deducted the number of cases upon which the seasonal curve is superimposed; in this way it is found that the three true "waves" comprise about 37, 210 and 153 cases respectively.

It is found, therefore, that although the three waves comprised such differing numbers of cases as those cited—the greatest about 6 times as large as the smallest—

34. Bjørneboe, M., and Brøchner-Mortensen, K.: Ugesk. f. læger **107**:715, 1945.

35. Jersild, M.: Ugesk. f. læger **107**:810, 1945; New England J. Med. **237**:8, 1947.

36. Alsted, G.: Am. J. M. Sc. **213**:257, 1947.

37. Petersen, H.: Nord. med. (Hospitalstid.) **16**:3509, 1942; Acta med. Scandinav. **107**:310, 1941.

the apices of the curves were the same, that is to say the curves are similar, which according to my theory signifies that the waves were not due to mutual infection but *must have been the result of variation either in the virulence or in the resistance.*

I would however add that before counting on this hypothesis, it would be highly desirable to have the figures for the two following years which, I understand, are also relatively high, and in addition to have the monthly figures for all 5 years as the quarterly ones are a bit too crude for the calculation.

To the reservation expressed by Petersen it should be added that even on the supposition that thyrotoxicosis is an infectious disease, it must be a difficult subject for mathematical treatment on account of its protracted course and the uncertainty of settling the time of onset of the disease.

Attempts at Transmission.—The attempt to transmit thyrotoxicosis experimentally from patients to animals (mostly dogs) has been made by a good many investigators (Soupault,[38] Boinet,[39] Pässler,[40] Schultze,[41] Pfeiffer [42] and Klose, Lampé and Liesegang.[43] The experiments, performed rather a long time ago, did not aim at the transmission of a possible infectious disease but were designed to investigate whether a toxic substance existed in cases of exophthalmic goiter the action of which could be detected in transmission experiments. The experimental material consisted of extracts, pulverized matter, expressed juice or living tissue from extirpated goiters and also exophthalmic goiters which were transferred by injection or transplantation to various experimental animals and, in 1 case (Schultze), to man. In some of the experiments immediate toxic symptoms which resembled those of exophthalmic goiter were noted, while in others a negative result was obtained. The experiments were of short duration, lasting only for a few days or weeks.

The attempt to transfer a possibly specific infective agent and thereby produce a true thyrotoxicosis corresponding to the disease which affects man has not been made. The possibility of producing thyrotoxicosis experimentally in animals in this way, even on the assumption that the disease is a specific infectious one, would scarcely be great. Spontaneous thyrotoxicosis has certainly been observed in dogs, horses, cattle, sheep and cats, but, according to the veterinary literature, it is extremely rare.

38. Soupault, cited by Klose, Lampé and Liesegang.

39. Boinet: Province méd. **37**:38, 1899.

40. Pässler, H.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **14**:330, 1905.

41. Schultze, K.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **17**:655, 1907.

42. Pfeiffer, C.: München. med. Wchnschr. **54**:1173, 1907.

43. Klose, H.; Lampé, A. E., and Liesegang, R. E.: Beitr. z. klin. Chir. **77**:601, 1912.

A number of isolated observations may be of some interest. Simmonds,[44] Kocher [45] and especially Sølling [46] found, by histologic examination of material from a toxic goiter, accumulation of lymphocytes and plasma cells in the interstitial tissue in the gland and interpret this as a sign of a state of chronic infection. The shift in the serum proteins has been briefly discussed by Houssay.[47] Among 305 patients with thyrotoxicosis Kalbak [48] found the blood sedimentation rate to be above 10 mm. per hour in 55 per cent, in 11 per cent of whom it was above 30 mm. per hour. The relative lymphocytosis which numerous investigations have revealed in thyrotoxicosis is a well ascertained phenomenon in a number of virus diseases.

The idea of thyrotoxicosis as entirely or partly caused by a specific infective agent is, as before mentioned, so alien to the mind that one is inclined to dismiss it forthwith, and a number of objections arise in rapid succession. Against this, however, the epidemics stand as "a brutal fact," of which the Danish one at any rate is substantiated and incontestable. The epidemic curve and some of the features of the epidemics are in favor of a specific infection, and if it were a question of some disease other than thyrotoxicosis the theory of a specific infection would presumably sound natural enough or even the only acceptable one. In this connection it may perhaps be recalled what a long time elapsed before it became possible to relinquish the idea that "catarrhal jaundice" was caused by a plug of mucus in the common bile duct in favor of the conception that the disease was epidemic hepatitis due to a specific virus.

Therefore, in spite of all that has been said to the contrary, it will be right henceforward, in a consideration of the causation of thyrotoxicosis, also to keep in mind that the disease might be entirely or in part caused by a specific infective agent of unknown nature and to include this theory as a starting point for future investigations.

SUMMARY

Some earlier observations on the epidemic occurrence of thyrotoxicosis are referred to. This is followed by a discussion of the Danish epidemic of the years 1942 to 1946 and of similar Norwegian and French epidemics. The possible cause of the temporary rise in frequency is discussed, and the hypothesis that a specific infective agent may be the cause of the epidemics of thyrotoxicosis is advanced.

44. Simmonds, M.: Deutsche med. Wchnschr. **37**:2164, 1911.

45. Kocher, A.: Arch. f. klin. Chir. **92**:442, 1910.

46. Sølling, H. A.: Kliniske studier over morbus Basedowiis aetiologi, pathogenese og behandling, Copenhagen, G.E.C. Gad, 1916.

47. Houssay, cited in A Series of Lectures on the Hypophysis, Foreign Letters (Buenos Aires), J. A. M. A. **101**:1168 (Oct. 7) 1933.

48. Kalbak, K.: Acta med. Scandinav., to be published.

LYMPHOSARCOMA OF THE GASTROINTESTINAL TRACT

With a Report of Twenty-One Cases

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LYMPHOSARCOMA of the gastrointestinal tract is of interest not only because of its rarity but because of the diagnostic difficulties and its difference in therapeutic response from other malignant lesions of the gastrointestinal tract.

We have confined our observations to those cases in which the lesion was primary in one or several portions of the gastrointestinal tract. The cases in which there was widespread involvement of the lymph nodes, even though the gastrointestinal tract was also involved, were excluded because it may be assumed that this was the disseminated type of lymphosarcoma with multicentric primary foci. It is likely, however, that in some of these cases the condition may have begun as primary gastrointestinal lesions, with subsequent metastasis to lymph nodes and other organs. If only the regional lymph nodes were involved, the condition was considered as a primary gastrointestinal neoplasm with spread to regional lymph nodes.

The gastric and intestinal localization of this neoplasm will be discussed separately.

GASTRIC LYMPHOSARCOMA

Incidence.—In the fifteen year period 1931 to 1946, 11 cases of primary gastric lymphosarcoma were observed. During this same period, 960 patients with carcinoma of the stomach were treated. This is a ratio of 1 lymphosarcoma to 88 carcinomas and is a somewhat higher ratio than that reported by McSwain and Beal,[1] who found 7 cases of lymphosarcoma to 384 cases of carcinoma, a ratio of 1 to 55. Warren

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1. McSwain, B., and Beal, J. M.: Lymphosarcoma of the Gastro-Intestinal Tract, Ann. Surg. **119**:108, 1944.

and Lulenski [2] found 1 lymphosarcoma to every 71 gastric carcinomas. In a review of their experience at the Mount Sinai Hospital of New York Varnis and Colp [3] reported 8 cases of lymphosarcoma among 250 cases of neoplasm of the stomach, or 3.2 per cent. This is an incidence nearly three times as great as ours. Renshaw and Spencer [4] and Phillips and Kilgore [5] expressed the opinion that sarcomas constitute about 1 to 1.5 per cent of all malignant neoplasms of the stomach; this is approximately in accordance with our experience. The rarity of the condition is attested to by the fact that many of the reports in the literature consist of 1 or 2 cases.

Age.—The ages of our patients varied from 26 to 57. Six of the patients were below 50 years of age, and the average of the group was 47. This is in agreement with the observation reported in the literature that lymphosarcoma occurs in younger persons than does carcinoma. However, a great deal of variation in regard to age is reported. Cash and Rappaport [6] reported a case of reticulum cell sarcoma in a 33 year old man. In the 7 cases reported by McSwain and Beal [1] the ages varied from 43 to 65. The series of cases reported by Rafsky and others [7] showed widespread age variations, the ages being from 19 to 80. Despite the fact that gastric lymphosarcoma does occur at the extremes of age, a neoplasm occurring in a younger person is more likely to be a lymphosarcoma than a carcinoma.

Symptoms.—The symptoms of lymphosarcoma of the stomach are not any more diagnostic than are the symptoms of gastric carcinoma. The question of whether the symptoms are sudden in onset or insidious and extending over a long period is an important one. The duration of symptoms before a diagnosis of lymphosarcoma was made showed a great deal of variation. The shortest period during which symptoms were complained of was three months. The longest period was twenty-four years. Only 4 patients had complaints of less than a year's duration, 1 each for three, eight, nine and ten months. The other 7 patients complained of symptoms for one, one and a half, three (2 patients), five,

2. Warren, S., and Lenski, C. R.: Primary Solitary Lymphoid Tumors of the Gastro-Intestinal Tract, Ann. Surg. **115**:1, 1942.

3. Varnis, H., and Colp, R.: Lymphosarcoma of the Stomach, Gastroenterology **1**:1022, 1943.

4. Renshaw, R. J. F., and Spencer, F. M.: Gastroscopy and Lymphoma of the Stomach, Gastroenterology **9**:1, 1947.

5. Phillips, J. R., and Kilgore, F. H.: Lymphosarcoma of the Stomach, Am. J. Surg. **31**:179, 1936.

6. Cash, I. I., and Rappaport, A. E.: Reticulum Cell Sarcoma of the Stomach, Gastroenterology **6**:40, 1946.

7. Rafsky, H. A.; Katz, H., and Krieger, C. I.: Varied Clinical Manifestations of Lymphosarcoma of the Stomach, Gastroenterology **3**:297, 1944.

eight and twenty-four years. In the cases in which symptoms were of many years' duration it may be doubted that the origin of the neoplasm coincided with the onset of symptoms. If that were not so, it must be postulated that the patients suffered from another condition and that

TABLE 1.—*Lymphosarcoma of the Stomach*

	Cases
Age Range:	
a. 25 to 30 yr.	1
b. 31 to 40 yr.	2
c. 41 to 50 yr.	3
d. 51 to 60 yr.	5
Average age: 47 yr.	
Site of Lesion:	
a. Along greater curvature	8
b. Along lesser curvature	2
c. Prepyloric region	1
Cell Types (Biopsy):	
a. Small cell type	5
b. Reticulum cell type	5
c. Undetermined	1
Types of Therapy:	
a. Gastric resection plus irradiation	4
b. Irradiation alone	7

TABLE 2.—*Lymphosarcoma of the Stomach*

	Cases
Length of Survival After Therapy:	
a. Gastric Resection plus Irradiation	
1. 6 mo.	1
2. 2 yr.	1
3. Over 6 yr.	2
Average: 46.5+ mo.	
b. Irradiation Alone	
1. Under 1 yr.	4
2. Over 2 yr.	2
3. 5 yr.	1
Average: 18.5 mo.	
Length of Survival According to Cell Types:	
a. Small Cell Lymphosarcoma	
1. Gastric Resection plus Irradiation	
(a) 6 mo.	1
(b) 2 yr.	1
(c) Over 6 yr.	2
Average: 46.5 mo.	
2. Irradiation Alone	
(a) 8 yr.	1
(b) 5 yr.	1
b. Reticulum Cell Lymphosarcoma	
1. Irradiation Alone	
(a) Under mo.	4
(b) 2 yr.	1
Average: 7.0+ mo.	

eventually lymphosarcoma developed. This will be discussed in greater detail later; however, it should be emphasized that a history extending over many years does not preclude the presence of lymphosarcoma.

Among the presenting complaints were symptoms of ulcer, relieved by the intake of food, postprandial distress not well relieved by food, belching, bloating, pain in the right upper quadrant, backache, vomiting,

sour stomach and pain in the lower part of the abdomen. Weight loss, was reported by 5 patients and varied between 17 (7.7 Kg.) and 35 pounds (15.9 Kg.). An abdominal mass was observed by 1 patient. Symptoms of gastrointestinal hemorrhage, either melena or hematemesis, were present in 6 of the 11 cases. This is a rather surprising finding since the neoplasm begins in the submucosa and may not involve the mucosa until later, or not at all, and bleeding into the lumen of the gastrointestinal tract should not be expected. Nevertheless, it was one of the most common presenting symptoms.

The presence of gastrointestinal hemorrhage in cases of lymphosarcoma is not emphasized in the literature. Moreton [8] stressed the ulcer type of pain. Rafsky and others [7] reported only 2 cases of hematemesis among their 12 patients. Varnis and Colp [3] claimed, from their experience, that hematemesis was unusual but melena frequent. In our series, both manifestations of bleeding were common. Hematemesis alone was seen three times, hematemesis and melena twice and melena alone twice.

It is important to discuss further the significance of symptoms of ulcer. Although these symptoms have occurred twice in our series, they have been emphasized by other observers. Since peptic ulcer is so common in the adult population, it may occur concomitantly with another disease of the gastrointestinal tract. This seemed likely in 1 of our cases, in which symptoms of ulcer had been recurrent since 1930. The patient was treated for an ulcer in 1933 and 1934, when the roentgenogram of the gastrointestinal tract was reported as showing a duodenal ulcer. In 1935 he had a recurrence of the symptoms of ulcer, with melena, but this time the gastrointestinal series showed a gastric neoplasm. Exploratory laparotomy revealed a tumor of the greater curvature; no mention was made in the operative report of whether duodenal scarring was noted. Did this patient originally have a duodenal ulcer which was followed by lymphosarcoma, even though the symptoms remained unchanged, or did he have a slowly growing lymphosarcoma which developed over a period of years?

Another patient complained of epigastric distress and occasional emesis of eight years' duration. In January 1940 he had an episode of melena and vomited some bright red blood. At this time a gastrointestinal series revealed the presence of the neoplasm (fig. 1). Except for the bleeding, there had been no change in the symptomatology, and it is difficult to determine the exact time when the neoplasm began. But one cannot entirely exclude the possibility that the neoplasm or some precursory lesion began eight years previously.

8. Moreton, R. D.: Gastro-Intestinal Lymphosarcoma: Diagnostic and Therapeutic Problems, Texas State J. Med. **42**:31, 1946.

One 48 year old patient came under observation in 1942 and reported epigastric symptoms since 1918. These consisted of vague epigastric pain, "gas pains" and sour eructations. Since 1928 there had been almost daily small emeses which occasionally contained blood. A 35 pound (15.9 Kg.) loss of weight was reported over a period of several years. This continuous history for twenty-four years renders it difficult to date the onset of the lymphosarcoma. Because there was no abrupt change in the symptomatology, one may speculate about whether the

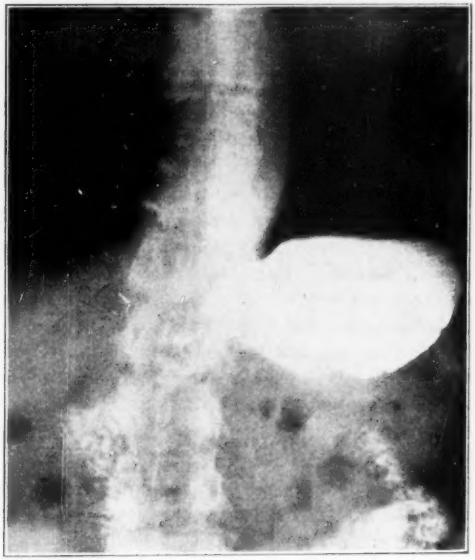

Fig. 1.—Roentgenogram revealing the deformity of the pyloric area before treatment.

gastric abnormality present over those years contributed to the pathogenesis of the lymphosarcoma.

Physical Findings.—The conspicuous feature about the physical findings is the frequency with which a mass is palpable. In 5 of the cases a mass was palpated in the epigastrium. In 1 case symptoms were present for about six months, and when the patient was first examined no mass was felt. Several weeks later a mass was distinctly palpated in the epigastrium, which underwent rapid and obvious enlargement within a short period of observation. In 4 cases the findings were noncontributory exe pt for evidence of loss of weight or of anemia. Tenderness in the

epigastrium was present in several patients. Hepatic enlargement was found in only 1 case, and in this case ascites was also detected. In no case were the peripheral nodes enlarged.

Laboratory Findings.—The presence of occult blood in the stools was a common finding, occurring in 7 cases. One additional patient undoubtedly had occult blood because he had hematemesis; however, he underwent gastrectomy before coming to Hines hospital. In only 3 cases did the stools contain no occult blood. This finding of occult blood in a submucosal lesion which does not involve the mucosa until late in the disease is rather surprising.

Anemia was a common finding but not as common as occult blood in the stools. The red blood cell count varied from 1,400,000 to 5,000,000. Five patients had red blood cell counts over 4,000,000, and 1 had a normal count of over 4,500,000. Four patients had counts below 3,000,000. A surprising finding is the lack of correlation between the anemia and the occult blood in the stools. Two patients who had anemia had stools which did not contain occult blood. It should be mentioned that blood may become benzidine negative in the gastrointestinal tract. It may thus be assumed that in these 2 cases there was also bleeding into the lumen of the gastrointestinal tract. One of the patients lost 17 pounds (7.7 Kg.) in weight, and it may be claimed that the anemia was on a nutritional basis. The other patient lost 35 pounds (15.9 Kg.) and certainly must have had a period of inanition.

The gastric acidity was on the low side of normal, and 2 patients had no free hydrochloric acid on gastric aspiration. No instance of hypersecretion was noted.

Roentgenography.—The difficulty in making a roentgenologic diagnosis of lymphosarcoma of the stomach is amply demonstrated in the literature. In most cases the diagnosis of carcinoma is made or reference to a neoplasm is noted. Occasionally, the stomach may be reported as normal or showing large rugal folds. The latter interpretation is of course most hazardous for the patient. Only occasionally does the roentgenologist interpret the findings correctly.

In the case reported by Cash and Rappaport [6] the lesion was called a carcinoma by the roentgenologist. Gordon and Greenebaum [9] reported a case in which there were suspicious roentgen signs, which disappeared and then reappeared. Moreton,[10] in his discussion of the roentgenologic features of gastric lymphosarcoma, enumerated the following possibilities:

9. Gordon, L., and Greenebaum, R. S.: Lymphosarcoma of the Stomach, Am. J. Digest. Dis. **12**:339, 1945.

10. Moreton, R. D.: Lymphosarcoma with Primary Manifestations in the Gastro-Intestinal Tract (Report of Seven Cases Studied Roentgenologically), Texas State J. Med. **41**:458, 1946.

(1) The stomach may be normal, (2) it may contain a gastric ulcer, (3) there may be diffuse infiltration of the entire stomach, (4) it may contain polypoid lesions which might be interpreted as a carcinoma and (5) an obstructive lesion may be present. Rafsky and his associates [7] reported a correct roentgenologic diagnosis in 4 of their 12 cases. In 6 cases the roentgenologist suspected neoplastic disease. They classified the roentgen features into four groups: (1) a filling defect with smooth margins, (2) localized types of lesions, (3) a diffuse type resembling linitis plastica and (4) giant rugal folds. Taylor [11] considered two or more filling defects and giant rugal folds as indicative of lymphosarcoma. Varnis and Colp [3] suggested that the presence of a large gastric ulcer crater in a young person is suggestive of lymphosarcoma. Of the 8 cases of gastric lymphosarcoma reported by McSwain and Beal,[1] in only 1 did the roentgenologist make the correct diagnosis; in the other 7 the diagnosis was carcinoma. From this brief review, it can be seen that the roentgenologist is not of too much assistance in arriving at the diagnosis of lymphosarcoma.

The roentgenologist did not fare any better in our series of cases. In only 1 case did he feel justified in reporting that the findings were compatible with lymphosarcoma. In 1 other the findings were suggestive enough to warrant the opinion that the appearance was consistent with lymphosarcoma. In 5 cases the roentgenologic diagnosis was carcinoma, and in 2 others the lesion was referred to as a neoplasm. No diagnosis was rendered in 1 case in which roentgen findings were so bizarre that no opinion was expressed. In this case it appeared to the fluoroscopist that the barium was leaving the gastric cavity through an opening in the greater curvature and entering an irregular cavity, perhaps the lesser peritoneal sac. Actually, the stomach was deformed by the tremendous neoplasm with a shelflike structure in its center which appeared to divide the stomach into two irregular cavities. In the case in which the diagnosis was made roentgenographically a large filling defect was seen on the greater curvature of the pylorus. The defect was extensive and appeared smooth, and there were no ulcerations or significant involvement of the mucosa. The opinion that lymphosarcoma was present was based on the lack of mucosal involvement despite the size of the tumor. In the case in which the findings were thought to be consistent with lymphosarcoma narrowing and loss of pliability of the prepyloric region were present, with intact rugal folds (fig. 2). The intact rugal folds are suggestive of an extramucosal tumor. The only diagnostic feature in our case in which a diagnosis of lymphosarcoma was considered roentgenographically consisted of a large mass that did not distort the mucosal pattern (fig. 3). In the case in which a negative report was rendered

11. Taylor, E. S.: Primary Lymphosarcoma of the Stomach, Ann. Surg. **110**:200, 1939.

at another hospital large rugal folds were present, which was disregarded at that time. This type of lesion is most hazardous from the point of view of roentgenologic diagnosis. When a filling defect is present, a

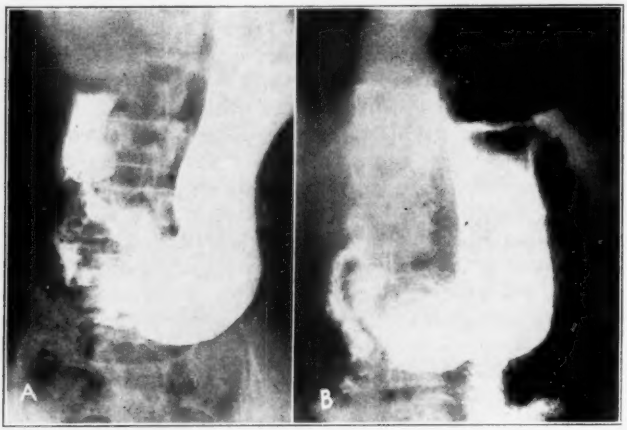

Fig. 2.—*A*, narrowing and loss of pliability of prepyloric area. Rugal pattern appeared to be intact. (Before treatment.) *B*, after irradiation.

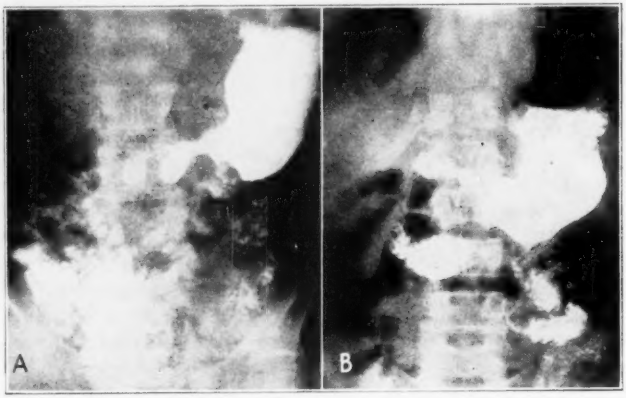

Fig. 3.—*A*, large filling defect along the greater curvature of the stomach (before treatment). *B*, after irradiation.

neoplasm will be diagnosed even though the type is undetermined. An ulcer will rarely be overlooked even though it may be thought to be benign. However, when the stomach is diffusely infiltrated without the formation of a localized mass, the impressions that it is normal or, at

most, contains large rugal folds may be rendered. If suspicion is not aroused and further work is not performed, the condition may progress undiagnosed until the patient is beyond assistance. In such cases gastroscopy would be of great aid.

Gastroscopy.—This procedure, while definitely of value, is by no means infallible. Schindler [12] emphasized an infiltrating mass with protruding hemorrhages while the mucosa is frequently intact as diagnostic of lymphosarcoma. Occasionally, all that may be seen gastroscopically are large rugal folds, and these may be mistaken for giant rugal folds.[4] However, if there is some rigidity and grayish nodules are seen, the suspicion that it is lymphosarcoma should be strongly entertained. In only 1 case in our series was gastroscopy performed. In this case the bizarre roentgen appearance which was not diagnosed as indicative of lymphosarcoma was present. Gastroscopically the rugal folds were huge and nonpliable and showed grayish nodules. Hence, the diagnosis of lymphosarcoma was hazarded in this case. At autopsy this was proved to be the correct diagnosis.

Pathologic Process.—The mass was located most frequently along the greater curvature, occurring there in 8 of the 11 cases. The lesser curvature and the prepyloric areas were involved in 1 case each. In 1 case the entire body of the stomach was involved. In 9 of the cases there was a sharply defined tumor mass; in 2 there was diffuse infiltration of the wall of the stomach. In the 26 year old patient the stomach was diffusely infiltrated and thickened to the point where it measured 2 cm. in some areas. In this case denudation of the surface epithelium over a large area was found at autopsy. However, before death no ulcer was seen roentgenographically or gastroscopically.

Involvement of the perigastric lymph nodes was found in 8 cases on exploratory laparotomy. In 1 case no regional lymph node or metastatic involvement was noted, and in 2 cases no observation in regard to this point was available. Metastasis to the liver was not observed in any of the cases in which surgical exploration was carried out.

The absence of widespread involvement of the lymph nodes or of spread to other organs indicated that the disease originated as a local neoplasm in the stomach.

The microscopic examination revealed that in 5 of these cases the mass was of the small cell type, the malignant lymphoma, whereas in 5 others it was of the large cell variety, or the reticulum cell type. This differentiation may be of some clinical importance, since the two types may show a different response to irradiation.

Prognosis and Treatment.—Since lymphosarcoma, or at least certain types, responds to roentgen therapy, the important question arises

12. Schindler, R.: Gastroscopy (The Endoscopic Study of Gastric Pathology), Chicago, University of Chicago Press, 1937.

of whether irradiation is superior or equal to surgical intervention as a therapeutic procedure. The corollary to this is whether combined surgical treatment and irradiation is not the most efficacious mode of therapy.

Despite the admitted sensitivity of lymphosarcoma to irradiation, surgical intervention seems to be the treatment of choice advocated in the literature. This view is expressed by Madding and Walters.[13] Warren and Lulenski [2] resected the tumor in 10 of their series of 12 cases. Taylor,[11] in a review of 152 cases in the literature, advised subtotal resection and irradiation; the tumor was resectable in about 50 per cent of these cases. McSwain and Beal [1] had favorable results with combined surgical treatment and irradiation or each separately. They treated 2 patients with irradiation alone, without recurrence, and 2 patients with combined therapy, without recurrence.

In our series 4 patients underwent gastric resection and irradiation. These patients survived an average of forty-six and a half months. One patient survived six months, and 1 each two, six and seven years. Among the 7 patients who received irradiation alone the average survival period was only 18.5 months. Only 1 of these patients survived five years; 2 survived over two years, and the other 4 lived less than one year. Thus in our series the patients treated by irradition alone survived for much shorter periods than those receiving combined therapy. However, this cannot be accepted as evidence that irradiation therapy is inferior to combined treatment since the condition of the patients not treated surgically was far advanced and inoperable.

The prognosis in regard to cell type reveals an interesting correlation. In 5 cases in which the tumor was of the small cell type the average length of survival was forty-four months, whereas in the cases in which it was of the reticulum cell type the average was only seven months. The patients who were treated by resection and irradiation survived more than sixty months each. With irradiation alone, 1 patient with malignant lymphoma survived thirty-six months. This is in agreement with the views expressed in the literature that the reticulum cell sarcoma does not respond to irradiation. However, Warren and Lulenski [2] take issue with this opinion.

The opinion that there is a relatively favorable response to the treatment of lymphosarcoma is not shared by all observers. Sugarbaker and Craver,[14] on reviewing 196 cases of lymphosarcoma, found that the lymphosarcoma involving the gastrointestinal tract had the most unfavorable prognosis. None of their patients who had primary involvement of the gastrointestinal tract survived five years, while the average length

13. Madding, C. F., and Walters, W.: Lymphosarcoma of the Stomach, Arch. Surg. **40**:120 (Jan.) 1940.

14. Sugarbaker, E. D., and Craver, L. F.: Lymphosarcoma: A Study of One Hundred and Ninety-Six Cases with Biopsy, J. A. M. A. **115**:17 (July 6); 112 (July 13) 1940.

of survival was only 6.6 months. In Taylor's [11] personally observed cases there was a better prognosis, with 2 patients surviving five years or better. Of the 14 patients described by Warren and Lulenski,[2] 7 were dead within one year, and the other 7 had no evidence of the disease one, two, three, four and nine years after treatment.

The prognosis in our series of cases is definitely better than that in cases of gastric carcinoma. In our series there were three "five year cures," and one of these involved a patient whose condition was considered inoperable. Such results could not be obtained in cases of gastric carcinoma, and they emphasize the importance of exploring apparently inoperable carcinomas in the hope that they may be lymphosarcomas and amenable to irradiation.

INTESTINAL LYMPHOSARCOMA

During this same period, 1931 to 1946, 10 cases of localized intestinal lymphosarcoma were observed. In 5 of these cases the tumor was located in the small intestine and in 5 in the large intestine. This neoplasm is therefore as rare and occurs with about the same frequency as that in the stomach. These findings are in agreement with those in the series reported by Warren and Lulenski,[2] who found lesions in the stomach in 14 cases, in the small bowel in 6 cases and in the colon in 8 cases; however, this series also included several cases of Hodgkin's disease. The rarity of the lesion is further attested to by the fact that up to 1943 only 404 cases had been reported in the literature.[15]

In a comparison of lymphosarcoma with carcinoma, the following interesting features were noted. In our experience, lymphosarcoma is as frequent in the small bowel as it is in the colon, although in the literature reference is made to the greater frequency in the small intestine.[3] During this same period, 1,489 patients with carcinoma of the colon (from the cecum to the anus) were treated, as compared to 5 with lymphosarcoma, a ratio of approximately 1 to 300. Twenty-two cases of carcinoma of the small intestine were observed during the same period, showing the rarity of this malignant growth, which yet is more than four times as frequent as lymphosarcoma in the same site.

The distribution of the lymphosarcoma in the small intestine in our series of cases was as follows: duodenum, 1 case; jejunum, 1 case; ileum, 2 cases, and jejunum and ileum, 1 case. Thus even in this small series the ileum is the commonest site of the lymphosarcoma, and the lesion becomes rarer cephalad until the stomach is reached. In fact, the incidence of ileal involvement is still greater, because in 2 cases of lymphosarcoma of the cecum the ileum was also involved. In the 3 other cases of colonic involvement, the lesion was situated in the ascending colon in 1 and in the rectosigmoid in 2.

15. Carache, H.: Primary Lymphosarcoma of the Intestines in a Boy of 7: Follow-Up of Seven Years, Am. J. Surg. **59**:601, 1943.

Symptomatology.—The symptomatology varied somewhat according to the site of the lesion but was not diagnostic in any of the cases. In the presence of a lesion of the duodenum nausea, emesis, and epigastric pain were prominent; occasionally small hematemeses were present. In the cases in which the lesions were in the jejunum and ileum, obstructive symptoms such as cramping abdominal pain, nausea, emesis, distention and constipation were notable. The obstructive symptoms were intermittent. Weakness and loss of weight were also reported. When the lesion was situated in the cecum, obstructive symptoms were absent, but anorexia and epigastric distress were usually predominant; aching in the right lower quadrant of the abdomen was also present. In the presence of a lesion of the ascending colon weakness and pain were prominent; the pain was abdominal and radiated to the sides and back. With the rectal lesions, obstipation and a sensation of rectal fulness were outstanding. Gross gastrointestinal hemorrhage was not present in any of these cases, in contrast to the cases of gastric lymphosarcoma.

Physical Findings.—The outstanding physical finding and the one which emphasized the presence of a neoplasm was an intra-abdominal mass. A mass was palpable in some portion of the abdomen in all but 2 cases of intestinal lymphosarcoma. The location of the mass was largely dependent on the area of the gastrointestinal tract involved. The mass was located in the right lower abdominal quadrant when the cecum and the terminal end of the ileum were involved. It was palpated in the left side of the pelvis when the rectosigmoid was the cite of involvement. In 1 case the mass was located in the upper part of the abdomen, and clinically it was thought that the transverse colon was involved, but actually the ascending colon, cecum and ileum were involved. A mass in the left upper quadrant was found in 1 case, with involvement of the midportion of the ileum. Of the 2 cases in which a mass was not palpated, the duodenum was the site of involvement in 1, and in the other ascites was present and masked the presence of the tumor, which otherwise might have been palpated

It should therefore be stressed that a mass becomes palpable early in the course of lymphosarcoma of the intestinal tract. In several cases the symptoms were present for only two months. This fact can be utilized in the differential diagnosis: If no mass is palpated in patients having abdominal symptoms for a considerable period, it may be concluded that the symptoms are not due to a lymphosarcoma of the intestine below the level of the duodenum.

The mass was usually movable and occasionally was as large as a grapefruit and was somewhat tender. Tympanites and borborygymus were noted in the patients during periods of partial obstruction.

The feature conspicuous by its absence was enlargement of the liver. The organ appeared to be of normal size, despite the advanced state of the disease. This is in marked contrast to the occurrence in

cases of carcinoma. Peripheral lymph nodes were not extensively involved, which shows that the disease may be localized in the gastrointestinal tract and involve distant lymph nodes only by metastasis. In only 1 case was there found involvement of a left inguinal node, and this was a case of extensive neoplasm of the rectosigmoid.

A temperature up to 103 F. shortly before death was present in 3 cases. However, a temperature up to 101 F. was present long before

TABLE 3.—*Lymphosarcoma of the Intestines*

	Cases
Age Range:	
a. 31 to 40 yr.	1
b. 41 to 50 yr.	2
c. 51 to 60 yr.	5
d. 61 to 70 yr.	2
Average: 52 yr.	
Site of Lesion:	
a. Duodenum	1
b. Jejunum	1
c. Ileum	2
d. Jejunum and ileum	1
e. Cecum	2
f. Ascending colon	1
g. Rectosigmoid	2
Cell Types (Biopsy):	
a. Small cell type	5
b. Reticulum cell type	5
Types of Therapy:	
a. Resection plus irradiation	4
b. Irradiation alone	4
c. Symptomatic	2

TABLE 4.—*Lymphosarcoma of the Intestines*

	Cases
Length of Survival After Therapy	
a. Resection plus Irradiation	
1. Under 1 mo.	1
2. 6 mo.	1
3. Over 4 yr.	1
4. Unknown *	1
b. Irradiation Alone	
1. Under 1 mo.	1
2. 3 to 5 mo.	2
3. Unknown *	1
c. Symptomatic	
1. 1½ mo.	1
2. 3½ mo.	1

* Patients left hospital; no follow-up was available.

death in 3 cases. Three patients were completely afebrile throughout their course of illness. Fever is thus a poor prognostic sign.

Laboratory Findings.—Severe anemia was not a conspicuous finding in these cases. The red blood cell count was above 4,000,000 in 3 cases and above 3,000,000 in all the other cases with the exception of 1, in which there was a count of 2,800,000. The white blood cell count was below 10,000 in all cases with the exception of 1, in which the count was 12,000.

Occult blood in the stool was present on the few occasions on which it was sought, but gross blood or tarry stools were not seen on any occasion.

Roentgenographic Findings.—The roentgenographic diagnosis was entirely erroneous in 3 cases. In 1 case in which there was ileal involvement a report of duodenal ulcer was submitted. The roentgenogram made after a barium enema revealed nothing significant and a study of the small bowel was not performed, and thus the area of involvement was not visualized. In another case, with involvement of the jejunum and ileum, the roentgenologist observed a filling defect in the duodenal bulb and the prepyloric portions of the stomach. In 1 case of duodenal lymphosarcoma pyloric obstruction and gastric retention were reported, but no opinion as to the cause of the obstruction was ventured. The roentgenographic evidence of obstruction disappeared after high voltage roentgen therapy of the abdomen, which proved that the gastric retention was a result of the lymphosarcoma. That the lesion was lower in the small bowel was proved at laparotomy.

No specific pathologic diagnosis was made by the roentgenologist in any of the cases. In 1 case the deformity of the cecum was considered to be due to extrinsic pressure, which it might well have been, because in addition to the cecal involvement there was also ileal involvement. In 1 case of cecal lymphosarcoma the condition was diagnosed as carcinoma. In another case in which involvement of the descending colon was present no pathologic changes were seen during the first examination but six weeks later a flat plate of the abdomen revealed gaseous distention of the bowel down to the middle of the descending colon. The diagnosis was an obstructive lesion at that point. In 1 case there was roentgenologic involvement of the transverse colon, which was thought to be neoplastic or inflammatory; the lesion, however, was actually in the jejunum, ileum and ascending colon. In a case in which there was involvement of the ileum and jejunum there was roentgenologic evidence of partial intestinal obstruction; no suggestion was ventured by the roentgenologist as to the origin of the obstruction.

Sigmoidoscopic Examination.—One patient with a rectal lesion was given sigmoidoscopic examination. A neoplastic lesion was observed obstructing the rectum a few centimeters above the rectal wall. A biopsy of this mass was made, and a diagnosis of lymphosarcoma was established.

Pathologic Process.—The lack of widespread metastatic involvement was as evident in these cases as in cases of lymphosarcoma of the stomach. This is also mentioned in the literature.[16] The regional lymph nodes,

16. Reifenstein, E. C.: Lymphosarcoma of the Gastrointestinal Tract, Rev. Gastroenterol. **4**:82, 1937. Ullman, A., and Abeshouse, B. S.: Lymphosarcoma of the Large and Small Intestine, Ann. Surg. **95**:878, 1932.

mesentery and omentum or contiguous structures were occasionally involved. Metastasis to the liver was not found. The incidence of the two cell types was equal, 5 cases of the small cell type and 5 of the reticulum cell type of lymphosarcoma being found. There was no correlation between the cell types and the location of the neoplasm.

Prognosis and Treatment.—The prognosis in this series was extremely poor. This was apparently due to the delay in diagnosis. Only 1 patient survived four and a half years after resection of a small cell lymphosarcoma of the ileum, despite the fact that symptoms antedated the diagnosis and the surgical treatment by two years. One patient received high voltage roentgen therapy as well as surgical treatment, but no follow-up was available. Another patient with rectal sarcoma diagnosed on proctoscopy received high voltage roentgen therapy alone; he likewise failed to report for follow-up.

The remaining patients died from ten days to five months after the diagnosis was established. One patient died ten days postoperatively, and this can be considered a surgical death. It is obvious that the diagnosis was established too late in these cases, and yet symptoms had not been present for too long a period. This suggests, as in gastric carcinoma, that there may be a considerable asymptomatic phase. Only 1 of these patients had symptoms for as long as one year; the others had symptoms only from six weeks to six months.

SUMMARY AND CONCLUSIONS

1. Eleven cases of primary gastric lymphosarcoma are reported.

2. Eighty-eight cases of gastric carcinoma were observed for each case of gastric lymphosarcoma.

3. Roentgenologic examination usually fails to establish a diagnosis; gastroscopy may be of help.

4. The prognosis of the small cell type of lymphosarcoma is better than that of the reticulum cell type.

5. Resection followed by irradiation is the treatment of choice.

6. The prognosis of gastric lymphosarcoma appears to be better than that of gastric carcinoma.

7. Ten cases of primary intestinal lymphosarcoma are reported.

8. Three hundred colonic carcinomas were seen for each lymphosarcoma, which shows that this neoplasm is extremely rare in the colon.

9. Intestinal lymphosarcoma appears to carry an extremely poor prognosis; no patient survived five years, and most died in less than six months.

CIRCULATORY AND DIURETIC EFFECTS OF THEOPHYLLINE ISOPROPANOLAMINE

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THERE is a surprising lack of factual information on which the employment of the xanthine diuretics for patients with cardiac disease may be based.[1] This is no doubt due to the widespread and almost exclusive use of mercurial diuretics in congestive failure of the circulation. The frequently heard opinion that theophylline is a useful adjunct in the treatment of heart disease has made it seem worth while to report studies which we have made on the immediate circulatory action and the diuretic effect of theophylline isopropanolamine,[2] a soluble salt of theophylline, and an organic base.

METHODS

To evaluate the immediate circulatory effects of theophylline isopropanolamine, the cardiac output was measured in 15 patients with heart disease before and after administration. The direct Fick procedure was used, with catheterization of the right side of the heart.[3] In addition to the cardiac output, the

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1. Marvin, H. M.: The Value of the Xanthine Diuretics in Congestive Heart Failure, J. A. M. A. **87**:2043 (Dec. 18) 1926.

2. Greenbaum, F. R.: New Water Soluble Theophylline Compounds, Am. J. Pharm. **109**:549, 1937.

3. Cournand, A.; Riley, R. L.; Breed, E. S.; Baldwin, E. deF., and Richards, D. W., Jr.: Measurement of Cardiac Output in Man Using the Technic of Catheterization of the Right Auricle or Ventricle, J. Clin. Investigation **24**:106, 1945.

procedures used made available the following data: optical records of the arterial and the intracardiac pressure,[4] oxygen consumption, pulmonary ventilation and the oxygen contents of the arterial and mixed venous blood. From these data, left ventricular work and peripheral resistance were calculated, with the use of conventional formulas. After control observations were made, 0.5 Gm. of theopropanol® (theophylline isopropanolamine) was injected intravenously in 20 cc. of solution during a period of two minutes. Thereafter, at varying intervals, the cardiac output was again measured. Pressure records were made every two or three minutes for a period of thirty to forty minutes.

The diuretic action of the drug on 21 patients in the medical wards of the University Hospital was studied. All had pitting edema of the extremities, while several also had effusion of fluid into the body cavities. Nineteen patients were suffering from congestive heart failure. Of these, 14 had arteriosclerotic heart disease, 1 pericardial effusion, 2 rheumatic heart disease with mitral stenosis and 2 advanced chronic nephritis with hypertension. The other 2 patients had hepatic cirrhosis with ascites.

Patients with cardiac disease were in moderate to severe failure. Most were on maintenance digitalis therapy and had failed in spite of this. These patients were continued on their usual dosage of digitalis after admission to the hospital. The few previously untreated patients had such severe heart failure that immediate treatment was mandatory. They were given either lantosid-C parenterally or digitoxin orally in a single full digitalizing dose on admission. All patients were confined to bed, on a low salt diet, and were allowed water ad libitum. Oxygen and sedatives were given as required.

The 2 patients with cirrhosis of the liver had been in the hospital several weeks under therapy, with no appreciable change in their condition, before this study was undertaken. Both had marked ascites, with some edema of the ankles. One had received repeated injections of meralluride ("mercuhydrin"), with questionable effect.

All data were recorded at 10 a. m. each day. The twenty-four hour urine output was measured and the patient weighed, when the condition permitted. An estimation of the degree of dyspnea and gross edema was recorded as 0 to 4 plus. Measurements of vital capacity were made at rather frequent intervals, and venous pressures were recorded, but these measurements have little bearing on this discussion of diuretic effect.

Diuretics were withheld for three days, or until a base line was established, when theopropanol® therapy was begun. Occasional patients were encountered who responded well to digitalis and rest in bed, requiring no diuretic. They, of course, were not included in this study. Such cases were rare, since only the patients with the more severe grades of failure were hospitalized. The patients with the most severe conditions were started with a deep intramuscular injection of 0.5 Gm. in 2 cc. of solution and then continued on oral medication of 0.2 Gm. three to four times daily. Occasionally intramuscular dosage was repeated during oral therapy.

4. Hamilton, W. F.; Brewer, G., and Brotman, I.: Pressure Pulse Contours in the Intact Animal: I. Analytical Description of a New High Frequency Hypodermic Manometer with Illustrative Curves of Simultaneous Arterial and Intracardiac Pressures, Am. J. Physiol. **107**:427, 1934.

TABLE 1.—*Changes Noted After Administration of Theophylline Isopropanolamine (0.5 Gm. Intravenously)*

Patient	Cardiac Output, %	Mean Arterial Pressure, Mm. Hg.	Peripheral Resistance, %	Heart Work	Right Heart Filling Pressure, Mm. Hg.	Pulmonary Arterial Pressure, Mm. Hg.		Pulse Rate	Stroke Volume, %	Per Cent Saturation Venous Blood	Respiratory Volume, %	Respiratory Rate/ Minute	Oxygen Consumption, Cc./ Minute
						Systolic	Diastolic						
I. K.†	+22	−7	−23	+	....	0	+1	+5	+16	+8.5	+42	+3	+7
A. B.†	+32	...	....	..	−5	..	...	+30‡	+4	+6.9	+80	+3	+45
L. B.†	+29	−1	−24	+	....	0	−1	+16	+14	+4	+3	+8	+42
W. H.†	+17	+8	−7	+	....	+1	0	+30‡	−15	+3.6	+32	+3	+15
J. B.*†	−3	+9	....	..	−1	..	...	+2	−2	−3.5	0	+3	+29
S. P.†	+22	...	....	..	−5.5	..	...	0	+21	+5	+3	+10	−27
A. W.†	+55	+16	....	..	....	..	...	+14	+23	+14	+110	−2	+13
C. L. S.*†	−4	...	....	..	....	..	...	....	....	−0.4	0	+4	−9
E. B.†	+25	−10	−24	+	....	6	0	+5	+19	+3	....	...	+51
C. B.†	+53	...	....	..	....	..	...	+78‡	....	+7.8	+100	+5	+81
J. G.	+27	+15	+2	+	....	−3	0	+22	0	−2.5	+46	0	+61
F. S.	+12	−8	−20	0	−6.5	..	...	−2	+12	−0.4	+11	+6	+27
J. B.	+72	+9	−36	+	+2.5	..	...	+1	+70	+0.5	+50	0	+187
J. B.*	+2	...	....	..	+3.5	..	...	....	0	+0.5	....	0	0
D. W.	+25	...	....	..	−2	..	...	+14	−10	+0.5	+36	+8	+40
D. W.*	+28	...	....	..	−2	..	...	+10	−6	+1.1	....	+7	+41
A. B.*	+2	...	....	..	....	..	...	....	....	−2	0	−3	+37
Average	+30	+3	−19	..	−2.4	..	...	+11	+13	+3.7 (5.2)†	+47	+4	+50

* These determinations were made after fifteen minutes had elapsed and are not included in the averages, which describe the immediate response.
† Congestive heart failure.
‡ Auricular fibrillation.

RESULTS

The immediate circulatory responses to intravenous injection of theopropanol® were uniform in all patients with decompensated cardiac disease regardless of the cause. Observations were made on 10 patients with decompensation and 5 with recompensation. All data are recorded in table 1. The most consistent finding was a definite increase in cardiac output, averaging 30 per cent for the series. This increase lasted only about fifteen minutes; in the determinations that were repeated at that time or later, the cardiac output had usually returned to the preinjection level. The increased cardiac output was accompanied with an increase in heart rate that averaged eleven beats per minute. The stroke volume increased 13 per cent, and the left ventricular work per beat increased in 6 of the 7 cases in which it could be estimated. There was no consistent change in the mean arterial pressure, and consequently the peripheral resistance fell during the response by an average of 19 per cent.

The increase in stroke volume and cardiac work occurred in spite of the fact that the right ventricular filling pressure decreased in 4 of the 5 cases. In the fifth case it rose slightly, but the increase in cardiac output was greater in this case (70 per cent) than in the others.

The drug acted as a respiratory stimulant, increasing the pulmonary ventilation and the oxygen consumption. The increase in the first lasted about as long as the increased cardiac output, but the increase in oxygen consumption outlasted the increase in cardiac output.

In contrast to the pronounced cardiorespiratory effects of the intravenous administration of the drug, no diuretic effects were noted. This was not true of intramuscular or oral administration.

As a preliminary step in estimating the diuretic action of theopropanol,® an effort was made to determine the oral dose at which gastrointestinal irritation or other unpleasant side reactions would occur. Fifteen randomly selected ward patients were given the drug in double the recommended oral dosage, i. e., 0.4 Gm. three times a day. Subsequently 5 of our patients with cardiac disease were given this dosage, making 20 in all. Of this number, 9 had nausea and vomiting, 6 on the first day of administration and 3 on the third day. Two others had mild nausea and headache. Thus 11 of the 20 could not tolerate this dosage level. When 7 of these patients were continued on 0.3 Gm. three times daily, only 1 continued to have nausea and vomiting, while 6 had no further difficulty. Of 20 patients taking 0.2 Gm. three to four times daily, 1 had mild nausea and headache, which persisted after changing from oral to intramuscular administration, suggesting central rather than local gastric action as the cause.

None of the 5 patients taking 0.4 Gm. three times a day experienced vomiting. Their diuretic response on this dose was no greater than

that at the 0.2 Gm. level. The maximum effect is obtained on a dose which rarely elicits undesirable side reactions.

The diuretic response of our patients has been graded as follows: good—twenty-four hour volume of urine more than double the baseline quantity and/or no other diuretic measures needed; fair—definite increase in urine output, but other diuretics also needed to clear edema, and poor—no demonstrable response.

The results are summarized in table 2. Twelve of the 21 patients showed good diuresis. One patient exhibited a definite response, but required a mercurial compound in addition to rid him completely of edema. In 8 of the 21 patients the results were unsatisfactory; 5 of these also failed to respond to a mercurial diuretic.

TABLE 2.—*Diuretic Response to Theophylline Isopropanolamine In the Presence of Edema**

	Arterio-sclerotic	Pericardial Effusion	Rheumatic	Hepatic Cirrhosis	Hypertension and Nephritis	Totals
Good	11	..	..	1	..	12 (57%)
Fair	1	..	..	..	..	1 (5%)
Poor	2	1	2	1	2	8 (38%)
Totals	14	1	2	2	2	21

* All patients had heart disease of the stated cause except 2 with cirrhosis of the liver.

It will also be seen from table 2 that most of the successful results were in the arteriosclerotic group. The drug is relatively ineffective for rheumatic heart disease and for hypertensive nephritis with edema.

COMMENT

The cardiovascular effects attributed to theophylline are direct cardiac stimulation and peripheral vasodilation. Our data offer confirmatory evidence on both these points. From the observation that intramuscular doses of theophylline produced an increase in cardiac output and work, with a decrease in diastolic heart size, Starr and others [5] concluded that the drug stimulates the heart. More recently, Howarth, McMichael and Sharpey-Schafer,[6] employing catheterization of the right side of the heart, have also concluded that the heart is stimulated because theophylline produced an increase in cardiac output in normal persons in spite of a decrease in right auricular pressure and

5. Starr, I.; Gamble, J. C.; Margolies, A.; Donal, J. S., Jr.; Joseph N., and Eagle E.: A Clinical Study of the Action of Ten Commonly Used Drugs on Cardiac Output Work and Size, on Respiration, on Metabolic Rate and on the Electrocardiogram, J. Clin. Investigation **16**:799, 1937.

6. Howarth, S.; McMichael, J., and Sharpey-Schafer, E. P.: The Circulatory Action of Theophylline Ethylene Diamine, Clin. Sc. **6**:125, 1947.

because, in the presence of congestive heart failure, the increase in cardiac output was greater than that which occurred when application of cuffs to the limbs brought about a similar decrease in filling pressure in the right side of the heart.

We have shown that there is a notable immediate increase in cardiac output, stroke volume and heart work accompanying a decrease in filling pressure in the right side of the heart, occurring in both the presence and the absence of signs of heart failure. Moreover there was no decided change in mean arterial pressure, some persons showing an increase in spite of a diminished peripheral resistance. These facts can be interpreted only as resulting from direct stimulation of the heart as well as from vasodilation.

Other observers [7] have noted little effect on heart rate. The fact that the 3 patients in our series in whom there was considerable acceleration were the only ones having auricular fibrillation may suggest a shortening of the refractory period in the ventricles or the conducting system.

In the presence of cardiac failure and pulmonary congestion, the usual elevation in pulmonary arterial pressure was seen. Use of theopropanol® did not lower the pulmonary arterial pressure significantly, which indicates that it had no effect on the degree of pulmonary congestion.

The respiratory changes noted may be of some importance. Although the drug produced an increased oxygen consumption, there was in every case of congestive failure a greater increase in cardiac output and hence a decrease in arteriovenous oxygen difference. Thus in every case in which there was decompensation the oxygen saturation of the mixed venous blood increased (average, 5.2 per cent). The change in the cases in which there was compensation, on the other hand, was inconsistent and insignificant. It has been postulated [8] that a diminished oxygen saturation of the venous blood is causally related to the signs and symptoms of heart failure. If this is true, the increase noted in these patients after administration of theophylline isopropanolamine would be a desirable effect, especially if it could be maintained by repeated intramuscular injections or oral administration.

The importance of the cause of the heart disease needs to be emphasized as a factor in the diuretic response to theophylline. Nearly all our good responses were in the arteriosclerotic group. Of the 34 patients treated with theophylline by Marvin,[1] about one third fell into each of

7. Starr and others.[5] Howarth and others.[6]

8. Briggs, A. P.; Fowell, D. M.; Hamilton, W. F.; Remington, J. W.; Wheeler, N. C., and Winslow, J. A.: Renal and Circulatory Factors in the Edema Formation of Congestive Heart Failure, J. Clin. Investigation **27**:810 (Nov.) 1948.

our three groups (good, fair and poor responses). The chief difference in our results lies in the greater number which we classify as "good," while fewer are considered "fair." The explanation for this is readily apparent, as Marvin's series included a far greater proportion of patients with rheumatic heart disease. Good results in cases of congestive failure of arteriosclerotic origin were also noted by Smith, Rathe and Paul,[9] using theophylline as the only medication. This is not a new finding, but it is one which deserves emphasis.

It is difficult to quantitate the extent of the diuresis, because the magnitude of response varies with the amount of edema. As the edema diminishes, so does the diuresis. However, a few figures may be useful in pointing out the extent of the diuresis that may occur in a susceptible patient after the use of theophylline isopropanolamine. Such figures are not presented as "average" or "usual" results but merely illustrate what we mean by a "good" response. On 7 occasions the 0.5 Gm. intramuscular preparation was given early in the course of treatment, while severe edema was still present. Loss of weight in the following twenty-four hours ranged from 1.5 to 4 Kg., with an average of 2.5 Kg. During oral medication only, the average twenty-four hour volume of urine for our patients was three times their average "base line" urine output.

Occasionally the effect of a mercurial diuretic was enhanced by prior administration of the test drug. Considerable potentiation of mercurial effect following intravenous injection of theophylline ethylenediamine has been reported by Herrmann and his associates[10] and by Goodman and his co-workers.[11] However, 5 of our 8 patients in whom theophylline failed also derived no benefit from parenteral mercurial therapy, so that we have had little opportunity to observe this effect. It should perhaps be noted that 3 of these 5 resistant patients died while in the hospital.

The patients with cirrhosis of the liver were included because retention of salt and water by the kidneys appears to contribute to the edema formation in this condition. One of these patients showed a prompt profuse diuresis during theophylline therapy. When intramuscular injections were given, his twenty-four hour output of urine

9. Smith, F. M.; Rathe, H. W., and Paul, W. P.: Theophylline in the Treatment of Disease of the Coronary Arteries, Arch. Int. Med. **56**:1250 (Dec.) 1935.

10. Herrmann, G.; Schwab, E. H.; Stone, C. T., and Man, W. L.: The Advantage of Alternating Vegetable and Metalic Diuretics in the Treatment of Edema of Congestive Heart Failure, J. Lab. & Clin. Med. **18**:902, 1933.

11. Goodman, J. I.; Corsario, J. F., and Stacy R.: Mercurial and Xanthene Diuretic in Chronic Congestive Heart Failure, Arch. Int. Med. **70**:975 (Dec.) 1942.

exceeded 6 liters; on oral medication it averaged 5 liters. The patient lost 32 pounds (14.5 Kg.) in twenty days. Diuresis diminished when the drug was withheld and increased on renewal of its administration. The other patient showed no benefit from this or any other treatment, and after a protracted illness he lapsed into coma and died.

SUMMARY

The immediate effect of intravenous injection of 0.5 Gm. of theophylline isopropanolamine is to produce a transient increase in the cardiac output, stroke volume, heart rate and cardiac work together with a lowering of the filling pressure of the right side of the heart. There is a consistent fall in peripheral resistance (vasodilation), but the fact that the increased cardiac output occurs with small or no fall in arterial pressure indicates that the myocardium is stimulated.

The drug also produced an increase in oxygen consumption and in pulmonary ventilation but no definite change in systemic or pulmonary arterial pressure.

Oral and intramuscular (but not intravenous) administration of the drug gave a satisfactory diuretic response in 11 of 14 cases of congestive failure of arteriosclerotic origin and in 1 of 2 cases of hepatic cirrhosis. The response in cases of rheumatic heart disease and of hypertensive nephritis was not satisfactory.

With effective doses of 0.2 Gm. three or four times a day, unpleasant reactions were seldom encountered.

EXPERIMENTAL PULMONARY INFARCTION

Abnormal Pulmonary Circulation as a Prerequisite for Pulmonary Infarction Following an Embolus

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PULMONARY infarction has never been produced consistently in experimental animals, although numerous investigators have attempted it.[1] Virchow, in 1856,[1k] observed that obstruction of branches of the pulmonary artery was not in itself sufficient to result in infarction. Karsner in 1912,[1f] using turnip seed emboli in dogs, concluded that some factor other than an embolus was necessary to cause infarctions. Most authors reported that obstruction of branches of the pulmonary artery is not sufficient to cause infarction, if infarction is defined as necrosis of pulmonary tissue.

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1. (*a*) Cohnheim, J., and Litten, M.: Ueber die Folgen der Embolie der Lungenarterien, Virchows Arch. f. path. Anat. **65**:99, 1875. (*b*) Dunn, J. S.: The Effects of Multiple Embolism of Pulmonary Arterioles, Quart. J. Med. **13**:129, 1919-1920; (*c*) The Effects of Multiple Pulmonary Embolism, Proc. Physiol. Soc., 1919-1920, p. v. (*d*) Fujinami, A.: Beiträge zur Entstehung der hämorrhagischen Infarkte der Lunge, Virchows Arch. f. path. Anat. **152**:61, 1898. (*e*) Hall, G. E., and Ettinger, G. H.: An Experimental Study of Pulmonary Embolism, Canad. M. A. J. **28**:357, 1933. (*f*) Karsner, H. T., and Ash, J. E.: Studies in Infarctions: I. Experimental Bland Infarction of the Lung, J. M. Research **27**:205, 1912-1913. (*g*) Mann F. C.: Pulmonary Embolism: An Experimental Study, J. Exper. Med. **26**:387, 1917. (*h*) Orth, J.: Künstliche Erzeugung des hämorrhagischen Lungeninfarctes, Verhandl. d. Gesellsch. deutsch. Naturf. u. Aerzte **69** (pt. 2):7, 1897. (*i*) Steinberg, B., and Mundy, C. S.: Experimental Pulmonary Embolism and Infarction, Arch. Path. **22**:529 (Oct.) 1936. (*j*) Underhill, S. W. E.: An Investigation into the Circulation Through the Lungs, Brit. M. J. **2**:779, 1921. (*k*) Virchow, R. L. K.: Gesammelte Abhandlungen zur wissenschaftlichen Medicin, Frankfurt a. M., Meidinger Sohn u. Comp., 1856.

An exception is the work of Steinberg and Mundy,[11] who produced occasional infarcts with employment of lead shot alone as emboli to occlude branches of the pulmonary artery. They, therefore, concluded that no factor except embolism is necessary to produce infarction.

Clinical observation long ago revealed that pulmonary infarction following an embolus occurred usually in patients who had concomitant pulmonary congestion or edema, e.g., hypostasis from lying in bed during convalescence from an operation or illness or from passive congestion due to left ventricular failure. More accurate confirmation of these observations was provided by autopsy studies, such as those by Hampton and Castleman.[2] These authors reported on 370 patients in whom pulmonary emboli were observed. Of the 40 per cent who were convalescing from an operation, 58 per cent exhibited pulmonary infarction. Another 30 per cent of the 370 patients had cardiac disease, and 90 per cent of these showed infarcts of the lung. The remaining 30 per cent were terminally bedfast patients who had received no surgical treatment and of these 62 per cent had demonstrable infarcts.

Sufficient nutrition to maintain the integrity of the pulmonary tissue when massive embolic obstruction of intralobar branches of the pulmonary arteries occurs would appear to come from an anastomosis of either pulmonary arteries in a lobe and/or of bronchial arteries. But when interference of either of these collateral sources of circulation occurs concomitant with pulmonary embolism necrosis of pulmonary tissue may ccur. It has been shown that the bronchial arteries anastomose with branches of the pulmonary arteries but the exact site is not definitely known.[3]

For these reasons we attempted to produce pulmonary infarction in dogs with normal and congested lungs, using emboli similar to those seen in clinical embolism and infarction, namely, intravascular thrombi.

METHOD

Part 1.—Pulmonary embolism was produced in 12 normal mongrel dogs under anesthesia, induced with pentobarbital sodium administered intraperitoneally in doses of 3 mg. per kilogram of body weight, by releasing blood clots from the jugular veins. The veins were previously doubly ligated, with ligatures placed

2. Hampton, A. O., and Castleman, B.: Correlation of Postmortem Chest Teleroentgenograms with Autopsy Findings, with Special Reference to Embolism and Infarction, Am. J. Roentgenol. **43**:305 (March) 1940.

3. (*a*) Ghoeryebb, A. A., and Karsner, H. T.: A Study of the Relations of Pulmonary and Bronchial Circulation, J. Exper. Med. **18**:500, 1913. (*b*) Henle, F. G. J.: Handbuch der systematischen Anatomie des Menschen, Braunschweig, F. Vieweg u. Sohn, 1866. (*c*) Miller, W. S.: The Arrangement of the Bronchial Blood Vessels: Preliminary Communication, Anat. Anz. **28**:432, 1906. (*d*) Schlaepfer, K.: Ligation of the Pulmonary Artery Combined with Resection of the Phrenic Nerve in Chronic Inflammatory Conditions, Especially Tuberculosis of One Lung, Am. Rev. Tuberc. **10**:35, 1924.

4 to 5 cm. apart. In the first few dogs this was done by exposing the vein under aseptic technic, but subsequently unsterile technic was used with passage of the ligatures beneath the skin and around the veins. The blood trapped in the segment between the two ligatures was coagulated by injection into each vein of 50 to 100 units of purified thrombin dissolved in 0.9 per cent sodium chloride solution. The clots, which formed almost instantly, were then freed by removing the proximal ligature and manually expressing them toward the heart. The dogs were autopsied three to ten days after release of the emboli and were killed by opening the chest, with the dog under anesthesia, and quickly removing the heart and lungs.

Part 2.—In 8 normal mongrel dogs alpha-naphthylthiourea (ANTU) was administered intravenously in doses of 2 mg. per kilogram of body weight just prior to release of the intravascular clots. (This purified drug was given in a dose of 4 mg. per cubic centimeter in a suspension of 6 per cent acacia and 0.9 per cent sodium chloride solution. This dose of ANTU was found by trial and

Results of Attempts to Produce Pulmonary Infarction in Dogs with Alpha-Naphthylthiourea

Emboli Alone—12 Dogs (48 hr. or more after release of emboli)		ANTU Alone (Controls) —4 Dogs (48 hr. or more after release of emboli)		ANTU and Emboli—8 Dogs (48 hr. or more after release of emboli)	
Lungs normal	12	Pulmonary edema	4	Lungs	
No emboli	5	Alone	2	Normal	1
Emboli in branches of pulmonary artery	7	With patchy intra-alveolar hemorrhage	2	Atelectasis	1
				Emboli present	
				Normal lung	3 (4 lobes)
				Alveolar necrosis (pulmonary infarction)	3 (4 lobes)
				Alveolar hemorrhage only (no necrosis)	3 (8 lobes)
				No embolus (absorption?)	
				Alveolar necrosis	1 (2 lobes)
				Alveolar hemorrhage	1 (1 lobe)
				Atelectasis	1 (1 lobe)

error on other dogs to be the one which gave fairly severe pulmonary edema and congestion but allowed a sufficient number of them to live long enough for infarction to occur.)

As controls, 4 dogs were given ANTU alone without the release of emboli. These dogs were autopsied also in three to ten days. In each dog, careful search was made for minute abnormalities in the lungs and for emboli of any size. Microscopic sections were made of any area of the lung which appeared at all abnormal.

The 24 dogs included in parts 1 and 2 represent those animals who did not die of sudden failure of the right side of the heart due to massive embolism and who survived the large dose of ANTU.

RESULTS

From the table it can be seen that infarction of the lung was not demonstrable in the 12 normal dogs in which vascular thrombi were released. Pulmonary congestion was produced in the 4 dogs receiving ANTU alone, but there was no gross or microscopic evidence of pulmonary infarction. Of the 8 dogs receiving ANTU just prior to the

release of emboli, 3 showed alveolar necrosis (pulmonary infarction) distal to emboli and 4 showed intra-alveolar hemorrhage without necrosis distal to the emboli.

COMMENT

We first attempted to produce experimental pulmonary embolism as like as possible to that seen clinically in man by using clots produced

Fig. 1.—Gross pulmonary infarction resulting from the combination of alpha-naphthylthiourea (ANTU) (to produce congestion) along with the release of an embolus.

intravascularly in the veins of the normal animal. Neither large nor small emboli observed at autopsy had produced infarcts distal to them. As did several previous investigators (using other forms of emboli), we observed that embolism alone does not result in infarction of the normal lung.

Clinical and autopsy observations suggested that pulmonary congestion or edema, or both, were prerequisites for infarction to follow an embolus to the lung. We employed ANTU, therefore, because it seemed to be the best method to produce pulmonary congestion and edema for the twenty-four to seventy-two hours required for true infarction to occur. This necessitated the use of large doses (2 mg. per kilogram administered intravenously) of ANTU. When smaller doses were employed, only transient pulmonary changes occurred, and with larger doses the dogs uniformly died within twenty hours. Even with the 2 mg. per kilogram dose, only about 30 per cent of the dogs lived long

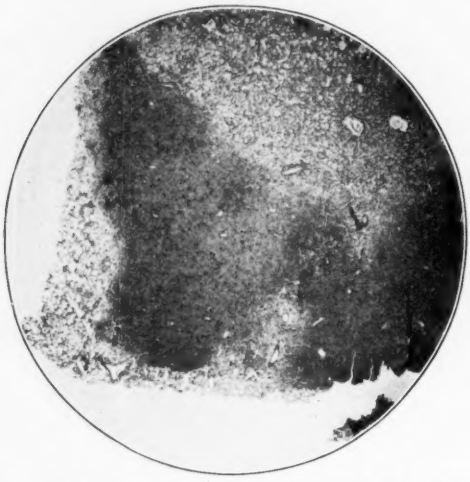

Fig. 2.—Microscopic appearance of the alveolar hemorrhage and necrosis (pulmonary infarction), secondary to the employment of alpha-naphthylthiourea (ANTU) and the release of an embolus.

enough (seventy-two hours) to fulfil the criteria for inclusion in our series. None of the dogs mentioned in the foregoing section were seriously ill at the time they were killed.

In those dogs subjected to ANTU alone patchy areas of intra-alveolar hemorrhage without necrosis occurred in some instances after three to ten days. Preliminary experiments showed that the pulmonary edema and congestion caused by ANTU had almost entirely subsided at the end of three to four days. In no dog did ANTU alone cause infarction.

True infarction was seen in four lobes among 3 dogs who had received ANTU prior to release of the emboli. Others of these dogs showed embolism but no change in the lung distally. Still others showed embolism with only intra-alveolar hemorrhage distally. We cannot say

whether this intra-alveolar hemorrhage represents the "incomplete infarction" reported by Hampton and Castleman, because similar lesions were observed in dogs as the result of ANTU alone.

True infarction was also seen in two lobes in which at autopsy no obstruction to the pulmonary artery or its branches to these lobes could be observed. We have no proved explanation for this phenomenon, but it suggests that clots large enough to cause obstruction to the infarcted area had been present but had dissolved by the time of autopsy. In preliminary work we observed, as have others, that blood clots lodging in the pulmonary arteries may be dissolved rapidly. In 5 of the 12 dogs in part 1 in which large blood clots were released from the jugular veins, evidence of emboli in the heart or in the pulmonary artery or its branches was not demonstrable after five days.

Apparently, obstruction of a pulmonary artery, or one of its branches, by an embolus does not cause infarction distally because blood supplied by the bronchial arteries or through anastomoses between intralobar pulmonary arteries is adequate to maintain nutrition. It appears, therefore, that, if circulation in the bronchial arteries and/or pulmonary intralobar anastomoses are interfered with by pulmonary edema or congestion, alveolar necrosis (infarction) results.

SUMMARY

Twenty-four dogs were used in an attempt to produce pulmonary infarction. No infarction resulted in 12 normal dogs in which intravascular clots were released. Pulmonary congestion was produced in 4 dogs by the administration of alpha-naphthylthiourea (ANTU), but no gross or microscopic evidence of pulmonary infarction was demonstrable. Of 8 dogs that received the drug prior to the release of emboli, 3 revealed pulmonary infarction distal to the embolism and 4 revealed alveolar hemorrhage distal to the embolism.

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ACUTE PHOSPHORUS POISONING

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THE RECENT observation of 2 fatal cases of acute phosphorus poisoning prompted an investigation of the incidence of phosphorus as a toxic agent and a review of the literature on the subject. Although at first glance its importance may seem slight, a further study of this condition brings to the foreground its serious nature and menace to the public health.

INCIDENCE

In the ten year period between 1934 and 1943, 14 patients with proved acute phosphorus poisoning were admitted to the Boston City Hospital, 7 of whom died, a mortality rate of 50 per cent. During this same period there were 1,443 admissions due to acute poisoning from other ingestants not including alcohol, with 90 deaths, a mortality rate of 6.2 per cent. Table 1 shows the incidence and mortality of the commonest toxic ingestants listed in order of their frequency. It will be noted that, although accounting for only 1 per cent of the total cases, phosphorus poisoning resulted in 7.1 per cent of the total deaths in this series and had the highest mortality.

In view of the easy accessibility of substances the ingestion of which, whether accidental, suicidal or homicidal, results in acute phosphorus poisoning and the striking paucity of literature on this subject, a review of the condition appears warranted at this time. A survey of the literature of this country from 1921 to the present revealed that, except for individual case reports appearing in the older pediatric literature,[1]

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1. (*a*) Stacy, W. C.: Dangers of Phosphorus in Fireworks, Correspondence, J. A. M. A. **77**:1514 (Nov. 5) 1921. (*b*) Corwin, A. E.: Report of a Case of Phosphorus Poisoning from Sucking a "Spit-Devil," New York State J. Med. **22**:475, 1922. (*c*) Salls, C. M.: The Menace of Phosphorus Fireworks, New York State Dept. Labor, Indust. Hyg. Bull. **1**:21, 1924. (*d*) Piersol, G. M., and Klemmer, R. N.: A Case of Acute Phosphorus Poisoning, Proc. Path. Soc. Philadelphia **27**:48, 1925. (*e*) Dwyer, H. L., and Helwig, F. C.: Phosphorus Poisoning in a Child from the Ingestion of Fireworks, J. A. M. A. **84**:1254 (April 25) 1925. (*f*) McIntosh, R.: Acute Phosphorus Poisoning: Report of a Case with Recovery,

the only reports of large series were those of 16 cases each by the American Museum of Safety in 1927 [2] and by Ladue and associates in 1944.[3] In addition, only a paragraph or two has been devoted to this subject in most recent standard texts on pharmacology and medical emergencies.[4] Although mentioned only briefly in this paper, chronic phosphorus poisoning was recently reviewed in detail by Heimann.[5]

HISTORICAL ASPECTS

Acute phosphorus poisoning occurred frequently in the last century and in the early part of this century when phosphorus was regarded as a therapeutic panacea,[6] and when the manufacture of match tips from yellow phosphorus (lucifers) was almost universal. It was not until 1942 that the use of the yellow phosphorus match was practically legislated out of existence by the placing of a high tax

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Am. J. Dis. Child. **34**:595 (Oct.) 1927. (*g*) McLean, S.; MacDonald, A., and Sullivan, R. C.: Acute Phosphorus Poisoning from Ingestion of Roach Paste: Report of a Fatal Case in a Child, J. A. M. A. **93**:1789 (Dec. 7) 1929. (*h*) Humphreys, E. M., and Halpert, B.: Acute Phosphorus Poisoning: Case Due to the Ingestion of Fireworks, Am. J. Dis. Child. **41**:354 (Feb.) 1931. (*i*) Blumenthal, S., and Lesser, A.: Acute Phosphorus Poisoning, ibid. **55**:1280 (June) 1938. (*j*) Sontag, L. W.: Acute Phosphorus Poisoning in an Infant Resulting from an Antirachitic Preparation, ibid. **56**:114 (July) 1938. (*k*) Brescia, M. A., and Dobbins, J. M.: Acute Phosphorus Poisoning: Report of a Case with Recovery, J. Pediat. **21**:378, 1942. (*l*) Chretien, T. E.: Acute Phosphorus Poisoning: Report of a Case with Recovery, New England J. Med. **232**:247, 1945. (*m*) Wentker, B. P., and Neubeiser, B. L.: Acute Phosphorus Poisoning: Case with Recovery, J. Missouri M. A. **28**:220, 1931. (*n*) Wertham, F.: Central Nervous System in Acute Phosphorus Poisoning, Arch. Neurol. & Psychiat. **28**:320 (Aug.) 1932. (*o*) Hann, R. G., and Veale, R. A.: A Fatal Case of Poisoning by Phosphorus with Unusual Subcutaneous Hemorrhages, Lancet **1**:163, 1910. (*p*) Dathe, R. A., and Nathan, D. A.: Electrocardiographic Changes Resulting from Phosphorus Poisoning, Am. Heart J. **31**:98, 1946.

2. Many Victims of Fourth of July Celebrations, editorial, Safety Engineering **54**:122, 1927. Salls.[1c]

3. LaDue, J. S.; Schenken, J. R., and Kuker, L. H.: Phosphorus Poisoning: A Report of Sixteen Cases with Repeated Liver Biopsies in a Recovered Case, Am. J. M. Sc. **208**:223, 1944.

4. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1941, p. 614. Beckman, H.: Treatment in General Practice, Philadelphia, W. B. Saunders Company, 1946, p. 903. Murphy, F. D.: The Diagnosis and Treatment of Acute Medical Disorders, Philadelphia, F. A. Davis Co., 1945, p. 449. Handbook of Medical Emergencies, Cambridge, Mass., Harvard University Press, 1947, p. 30.

5. Heimann, H.: Chronic Phosphorus Poisoning, J. Indust. Hyg. & Toxicol. **28**:142, 1946.

6. (*a*) Grollman, A., and Slaughter, D.: Cushny's Pharmacology and Therapeutics, ed. 13, Philadelphia, Lea & Febiger, 1947, p. 188. (*b*) Gould, G. M., and Pyle, W. L., in Sajous, C.: Cyclopedia of Practical Medicine and Surgery, Philadelphia, F. A. Davis Company, 1899, p. 471.

on its manufacture or sale and by laws against the export or import of such matches.[7] At present, nontoxic phosphorus sesquisulfide (P_2S_3) is used in matchheads. "Safety matches" have no phosphorus on the sticks, only red phosphorus on the striking surface in addition to other innocuous substances. In China and Japan, however, where the sale of yellow phosphorus matches is still allowed, the number of cases of acute phosphorus poisoning has increased.[8]

In the early twenties there were many reports of acute phosphorus poisoning in children as the result of the ingestion of firecrackers.[9] In addition, approximately 5 per cent of workers handling yellow phosphorus in the manufacture of fireworks had "phossy jaw"—

TABLE 1.—*Incidence and Mortality of the Commoner Toxic Ingestants, Excluding Alcohol; Boston City Hospital, 1934 to 1943*

Ingestant	No. of Cases	No. of Deaths	Mortality, %
Barbiturates	526	42	8.0
Iodine	210	4	1.9
Range oil, kerosene, turpentine	132	0	0.0
"Sulfonaphthol"; "lysol"	126	5	4.0
Paraldehyde	57	1	1.9
Mercury bichloride	53	6	11.3
Potassium permanganate	45	1	2.2
Bromides	35	2	5.7
Insecticides (chiefly sodium fluoride)	26	7	27.0
Lye	24	2	8.3
Ammonia water	22	1	4.5
Rat poison (contents unidentified)	20	0	0.6
Morphine	20	4	20.0
Merbromin	15	0	0.0
Phosphorus	14	7	50.0
Methyl salicylate	14	4	28.6
Other salicylates	12	0	0.0
Arsenic compounds	12	3	25.0
Carbon tetrachloride	12	4	33.3
Others (strychnine; hydrochloric, nitric and sulfuric acids, oxalic acid, camphor liniment, chloral hydrate, chloroform and others)	82	4	4.9
	1,457	97	6.6

a form of chronic phosphorus poisoning resulting in a disfiguring necrosis of the mandible.[10] For these reasons, a federal investigation of this hazard resulted in a voluntary agreement ending the use of phosphorus in the making of fireworks.[11]

7. Public Health Law No. 118 (H. R. 20842), United States Statutes at large of the 62nd Congress, April 19, 1942, vol. 37, pt. 1, p. 81.

8. Kiang, P. C.: Acute Phosphorus Poisoning, China M. J. **40**:1091, 1921. Read, B.: Phosphorus Poisoning, Nat. M. J. China **12**:46, 1926.

9. Salls.[1c] Dwyer and Helwig.[1e] Humphreys and Halpert.[1h]

10. Wells, G. H.: Case of Chronic Phosphorus Poisoning, M. Clin. North America **10**:95, 1926. Hamilton, A.: Industrial Poisons in the United States, New York, The Macmillan Company, 1925.

11. Ward, E. F.: Phosphorus Necrosis in the Manufacture of Fireworks and in the Preparation of Phosphorus, Bulletin 306, United States Department of Labor, Bureau of Labor Statistics, 1926.

PROPERTIES AND PREPARATIONS

The only form of phosphorus with which this paper is concerned is elementary phosphorus which, apart from its radioactive preparations, has no use at present in clinical medicine.

Phosphorus as the element does not occur free in nature. It is usually found as the phosphate, from which it is extracted by electrolytic methods. Elementary phosphorus is found in two forms: Amorphous or red phosphorus is nonvolatile, insoluble, unabsorbable and, therefore, nontoxic when taken by mouth. Since it may contain traces of yellow phosphorus (up to 0.6 per cent), large doses of it may have adverse effects. It is toxic when given intravenously, probably because of its conversion into yellow phosphorus.[12] Yellow phosphorus (to which this paper will refer unless otherwise noted) is an active poison which is practically insoluble in water; however, it diffuses through water as a vapor and forms a dilute colloidal solution. It is soluble in fats and in bile and is, therefore, absorbed from the intestine and from subcutaneous injections, especially when administered in a finely divided form. Toxic quantities may be absorbed from the skin and by inhalation of phosphorus vapors. It is excreted in the oxidized form as hypophosphoric acid, but its fate is imperfectly known. Although it oxidizes readily in the air, its oxidation in the blood requires days. It may have an inhibitory action on oxidizing ferments similar to that of hydrocyanic acid. During its action, it exists unchanged in the organs and in the expired air.[12] Some of its intermediary metabolic effects are discussed later.

When ingested in a finely divided condition or in solution in oil, phosphorus in very small quantities can give rise to toxic symptoms.[6a] In fact, as little as 15 mg. of yellow phosphorus can produce untoward symptoms,[13] and fatal poisoning in man has resulted from doses of 0.05 to 0.1 Gm., or about 1 mg. per kilogram of body weight.[10] Recovery has been reported after the ingestion of 200[14] and 400 mg.[11] Webster[15] and Wertham[16a] were of the opinion that those who are subject to nervous diseases may be somewhat more susceptible than others.

The commonest source of phosphorus as a poison is in the form of rat poisons as pastes, powders or seeds, and roach and vermin powders. These contain from 1 to 4 per cent yellow phosphorus and

12. Sollmann, T.: A Manual of Pharmacology and Its Application to Therapeutics and Toxicology, ed. 5, Philadelphia, W. B. Saunders Company, 1936.

13. McNally, W. D.: Toxicology, Chicago, Industrial Medicine Publishing Co., 1937.

14. Smith, S.: Forensic Medicine, ed. 6, Boston, Little, Brown & Company, 1938, pp. 473-477.

15. Webster, cited by Lawrence and Huffman.[16a]

can be almost universally purchased at drug, hardware or grocery stores. In the past few years there have been rare reports of poisoning resulting from the use of phosphorus as an abortifacient.[1m]

CLINICAL PICTURE

The signs and symptoms of acute phosphorus poisoning are classically divided into three stages. The clinical picture will, of course, vary depending on the amount ingested, the age of the patient, the time elapsed since ingestion, the treatment given and other factors.

First Stage.—This begins shortly after the ingestion of the poison, but in some patients its onset is delayed for several hours. It apparently represents the irritating effects of the phosphorus on the gastrointestinal tract. The symptoms are those of severe gastroenteritis—abdominal pain, nausea, vomiting and shock. Diarrhea occurs in about 35 per cent of patients. The breath, vomitus and, in the presence of diarrhea, the feces have an unmistakable odor of garlic. This sign is an extremely valuable one, as it is practically pathognomonic of phosphorus poisoning. Rarely does chronic arsenic poisoning result in an odor of garlic. Lewisite gas poisoning and ingestion of garlic must of course be ruled out. Another important observation is the presence of luminescent vomitus and feces; this occurs only in phosphorus poisoning. There may be actual phosphorus gas eructations from the mouth and nose, and thirst is intense. This stage usually lasts six to eight hours.

Second Stage.—If the patient does not die in the first stage, there ensues a symptom-free period of apparent improvement usually lasting from one to three days but occasionally as long as ten days. During this period, the patient generally regains consciousness and appears to be on the road to recovery.

Third Stage.—During the third stage there is a systemic toxemia due to the action of the absorbed poison. It is first manifested by nausea and vomiting, diarrhea and abdominal tenderness, especially over the liver. Massive hematemesis may occur. In this stage, the liver enlarges rapidly and icterus develops. There may be hemorrhages into the skin, mucous membranes and viscera. Leukopenia may be present.[11] Lawrence and Huffman[16] called attention to the increase in monocytes. Renal damage is evidenced by oliguria, hematuria and casts. Leucine, tyrosine and cystine crystals may be seen in the urinary sediment, and the urine may even be phospho-

16. Lawrence, J. S., and Huffman, M. M.: (*a*) Increase in the Number of Monocytes in Blood Following Subcutaneous Administration of Yellow Phosphorus in Oil, Arch. Path. **7**:813 (May) 1929; (*b*) Fatty Changes in the Kupffer Cells in the Liver of the Guinea Pig in Phosphorus Poisoning, ibid. **7**:809 (May) 1929.

rescent.[17] The electrocardiogram shows changes in the T waves and S-T segments of leads 1, 2 and 4,[1p] which, in the opinion of Katz, may be due to the development of cardiac ischemia.[18] Local alterations in conduction may be the result of direct action on the nodal and conduction tissues. This pattern simulates the changes seen frequently in acute glomerulonephritis,[19] after inhalation of nicotine in certain persons [20] and in severe anemia.[21] Central nervous system involvement often results in coma, delirium or convulsions. Death may be due to profound irreversible shock, hepatic failure, central nervous system damage or massive hematemesis.

Recovery or death may occur in either stage 1 or stage 3, although recovery from stage 3 is unusual. Of the 16 patients reported on in this paper, 6 recovered from stage 1 (37.5 per cent), 1 recovered from stage 3 (6.3 per cent), 4 died in stage 1 (25 per cent) and 5 died in stage 3 (31.3 per cent).

REPORT OF CASES

Table 2 gives a résumé of the 16 cases of acute phosphorus poisoning reported in this paper. The 2 cases observed recently and the 1 with recovery from stage 3 are reported in detail.

CASE 15.—L. J., a 19 year old cashier, was admitted to the First Medical Service of the Boston City Hospital on Dec. 15, 1946. No history was obtained on entry. According to information received later, the patient ingested about ⅓ ounce (9 Gm.) of a rat and roach paste containing 2.5 per cent white phosphorus and 97.5 per cent inert substances about three hours prior to admission. This is the equivalent of 230 mg. of phosphorus. Almost immediately after ingestion, the patient experienced violent nausea, vomiting and profuse perspiration. She appeared restless and at times delirious. The police were summoned, and the patient was hospitalized.

Physical examination on admission revealed a well developed and nourished young white woman who, although extremely weak and drowsy, could be roused and made to respond to questioning. Her temperature was 97.2 F.; the pulse was 120 and of poor quality, and respirations were 24 per minute. The blood pressure reading could not be obtained. The skin was cold and clammy, and there was cyanosis of the lips and nailbeds. The breath had a definite odor of garlic.

17. Rabinowitch, I. M.: Treatment of Phosphorus Burns, Canad. M. A. J. **48**:291, 1943. Oliver, T.: Conquest of an Occupational Disease: Phosphorus Poisoning in Lucifer Match Making, J. Roy. Inst. Pub. Health & Hyg. **1**:660, 1938.

18. Katz, L. N.: Textbook of Electrocardiography, Philadelphia, Lea & Febiger, 1941, p. 253.

19. Master, A. M.; Jaffe, H. L., and Dack, S.: The Heart in Acute Nephritis, Arch. Int. Med. **60**:1016 (Dec.) 1937. Katz.[18]

20. White, P. D.: Heart Disease, ed. 2, New York, The Macmillan Company, 1940, p. 386.

21. Graybiel, A., and White, P. D.: Electrocardiography in Practice, Philadelphia, W. B. Saunders Company, 1941, p. 160.

TABLE 2.—*Résumé of 16 Cases of Acute Phosphorus Poisoning*

Case No.		Age, Yr.	Ingestant	Time Elapsed Before Admission to Hospital	Laboratory Data	Course in Hospital	Stage
1	M. K.	46	Rat poison	3 days	15,150 white blood cells	Died 9 hr. after admission	3
2	P. C.	51	Rat poison	1 hr.	Reported in detail	Recovered	3
3	B. O.	1	20 safety matches	½ hr.		Discharged well in 2 days	1
4	J. D.	63	Rat poison	12 hr.		Died 3 hr. after admission	1
5	M. C.	76	Rat poison	Hours		Died 5 min. after admission	1
6	J. F.	20	Rat poison	4 days	3,100 and 3,600 white blood cells, with 66 to 80 polymorphonuclear leukocytes, 14 to 16 lymphocytes and 20 to 4 monocytes; icterus indexes, 130 and 120	Died 4 days after admission	3
7	M. H.	1	Matches	3 hr.		Died 1 day after admission	1
8	E. L.	5	Rat poison	1 hr.	21,750 white blood cells, with 54 polymorphonuclear leukocytes, 46 lymphocytes; 74 mg./100 cc. free bile salts	Discharged well on 12th day	1
9	M. L.	3	Rat poison	1 hr.	9,650 white blood cells, with 67 polymorphonuclear leukocytes, 33 lymphocytes	Discharged well on 9th day	1
10	F. C.	1	Rat poison	1 hr.	15,500 white blood cells, with 30 polymorphonuclear leukocytes, 62 lymphocytes, 8 eosinophils	Discharged well on 8th day	1
11	A. W.	2	Cockroach powder	1 hr.	6,900 white blood cells, with 70 polymorphonuclear leukocytes, 29 lymphocytes, 1 monocyte	Discharged well on 3d day	1
12	F. H.	3	Rat poison	1 hr.		Discharged well on 2d day	1
13	G. M.	22	Rat poison	14 hr.	3,950 white blood cells; icterus index, 100	Died 6 days after admission	3
14	D. M.	56	Rat poison	2 hr.	11,000 white blood cells, with 71 polymorphonuclear leukocytes, 13 lymphocytes, 16 monocytes; icterus index 60; prothrombin time, 80 sec.; cephalin flocculation test reaction, 4 plus	Became jaundiced on 5th day; died on 11th day	3
15	L. J.	19	Rat poison	3 hr.	Reported in detail	Died 5 hr. after admission	1
16	U. C. M.	?	? rat poison	Hours	Reported in detail	Died 54 hr. after admission	3

Examination of the head and neck showed nothing abnormal. The lungs were clear. The heart sounds were distant and of poor quality. Results of examination of the abdomen, extremities and nervous system were not remarkable.

Laboratory studies revealed a hemoglobin concentration of 14 Gm. and 16,000 white blood cells, with 48 per cent polymorphonuclear leukocytes, 50 per cent lymphocytes, 1 per cent monocytes and 1 per cent eosinophils. The reaction of the blood to the Hinton test was negative. Nonprotein nitrogen measured 31 mg. per hundred cubic centimeters. The stool was soft and brown, and the guaiac test showed absence of hemoglobin.

The patient's stomach was immediately lavaged, with the use of a large bore rubber suction tube and 5,000 cc. of a solution of sodium bicarbonate. One ounce (30 Gm.) each of magnesium sulfate, liquid petrolatum and magnesia magna was left in the stomach. A profuse watery diarrhea developed. Five per cent solution of glucose in water, 1,500 cc., was administered intravenously, followed by 1,500 cc. of isotonic sodium chloride solution, together with nikethamide, caffeine and calcium gluconate. Administration of oxygen was begun. She remained in a state of shock, the cyanosis becoming progressively severe and the respirations more shallow. She died five hours after her admission.

The diagnosis of the medical examiner and chemist was acute phosphorus poisoning. This patient is considered typical of the group who died during stage 1.

CASE 16.—U. C. M., a young Negro man, was admitted to the First Medical Service of the Boston City Hospital in a comatose condition after being found unconscious in his room. No accurate history could be obtained. About twelve hours prior to entry he had been seen conscious, although "appearing ill."

Physical examination on admission revealed a well developed and nourished Negro who was unconscious and responded only slightly to painful stimuli. There was a definite odor of garlic to the breath, and at one time phosphorescent eructations could be seen emanating from the mouth and nose. His temperature was 97.4 F. by axilla; the pulse was 108 and respirations 32 per minute and shallow. The blood pressure was 106 systolic and 70 diastolic. The results of the remainder of the physical examination were essentially normal.

Laboratory studies on admission revealed urine with a specific gravity of 1.014, negative reactions for albumin, sugar, bile or acetone and a normal sediment. Hemoglobin measured 12 Gm.; red blood cells numbered 3,750,000 and white blood cells, 5,000, with 76 per cent polymorphonuclear leukocytes, 21 per cent lymphocytes and 3 per cent monocytes. The reaction to the blood Hinton test was negative. Carbon dioxide-combining power was 31 volumes per cent and blood chlorides 94 milliequivalents. The stool was brown and soft, and the guaiac test showed no hemoglobin present.

Because of the odor of garlic to the breath, phosphorus poisoning was suspected, but poisoning by arsenic and fluoride could not be ruled out. On admission the patient's stomach was lavaged with 1,000 cc. of magnesium oxide. The aspirated material had a strong odor of garlic and fluoresced in the dark. His stomach was successively lavaged every half-hour thereafter for two hours with 1,500 cc. of magnesium sulfate, 100 cc. of hydrogen peroxide, 300 cc. of magnesium oxide and 250 cc. of cupric sulfate. In the first three hours he received a total of 3,000 cc. of isotonic sodium chloride solution intravenously, with 40 cc. of calcium gluconate and 1,500 cc. of 5 per cent solution of glucose in water, together with caffeine and nikethamide. One hour after entry he received 180 mg. of 2,3-dimercaptopropanol (BAL) intramuscularly, and 200 mg. was administered intramuscularly thereafter every four hours for ten doses. He also received 50,000 units of penicillin intramuscularly every three hours and was given oxygen by nasal catheter.

On this vigorous regimen the patient responded slowly. His pulse varied between 88 and 100, and the blood pressure between 96 and 110 systolic and 70 and 80 diastolic. In the first ten hours he received a total of 9,000 cc. of fluid intravenously and had a urinary output of 6,000 cc. His lungs remained clear, and there was no evidence of edema. No scleral icterus was ever noted.

BAL, penicillin and additional fluids intravenously, with vitamins, nikethamide and caffeine, were continued. At the end of twenty-four hours, he was conscious and seemed to understand when spoken to, but was uncooperative. Laboratory studies at this time revealed a *2* plus reaction for albumin in the urine. Nonprotein nitrogen measured 47 mg., carbon dioxide-combining power, 33 volumes per cent, blood chlorides, 91 milliequivalents and creatinine, 1.4 mg. per hundred cubic centimeters. There was a *2* plus reaction to the cephalin flocculation test.

His condition remained essentially unchanged until approximately fifty-four hours after admission, at which time he had a massive hematemesis. Blood transfusions were started immediately; but the blood pressure dropped precipitously; the pulse became imperceptible, and the patient died.

The diagnosis of the medical examiner and chemist was acute phosphorus poisoning. There was pronounced fatty infiltration of the liver. This patient is considered to have died during the early part of stage *3*. Interestingly enough, he had an inorganic phosphorus level of *2.96* mg. per hundred cubic centimeters of blood. Although seemingly paradoxic, other authors observed such levels also. The patients of Blumenthal and Lesser,[11] McIntosh [17] and McLean and associates [18] had blood phosphorus levels of *2.2*, 3.4 and *2.7* mg. per hundred cubic centimeters, respectively. None of these patients had any evidence of rickets. McLean expressed the view that these low phosphorus levels might be due to an inability of the body to metabolize carbohydrates properly.

The following patient is reported on because he represents the only one in this series who recovered from stage *3*.

CASE *2*.—P. C., a 51 year old white man, was admitted to the Boston City Hospital on Jan. 19, 1935. On Dec. 31, 1934, he had ingested an unknown amount of a rat poison containing 2.5 per cent phosphorus and was admitted to another hospital. On that admission he was acutely ill, complained of abdominal pain, nausea and vomiting and had an odor of garlic to his breath. His stomach was lavaged shortly after entry, and he apparently became asymptomatic rapidly. On his seventh day in the hospital, icterus was noticed, and on his twentieth day he was transferred to the Boston City Hospital.

Results of physical examination at the time were normal except for icterus of the skin and scleras. The liver was not palpable at any time. Laboratory studies included many urinalyses, the results of which were entirely normal, including those of tests for bile. The urinary urobilinogen was normal. His hemoglobin concentration was 70 per cent; red blood cells numbered 3,850,000 and white blood cells 9,200, with normal differential count and smear. The blood Kahn reaction was negative. Nonprotein nitrogen was 23 mg., blood calcium 11.6 mg. and blood phosphorus, 4.3 mg., per hundred cubic centimeters. On admission his icterus index was 60.

The patient was treated with a high carbohydrate, low fat diet and supplementary vitamins. Gradual improvement was noted, and his icterus cleared. He was discharged home from the hospital on his forty-eighth day. An attempt to follow up this patient was unsuccessful.

PATHOLOGIC OBSERVATIONS

The pathologic modifications vary with the stage in which death occurs. In stage 1 the changes consist usually of an acute esophagitis

and gastroenteritis. The gastrointestinal contents have an intense garlicky odor and may fluoresce in the dark.

Fatty infiltration is a striking observation in acute phosphorus poisoning and begins early. Numerous fat globules appear in the cells of many organs, notably the liver, kidneys, stomach, intestine, small arteries and skeletal muscles.[17] The fat is probably transport fat which is deposited in the organs, starting as a cloudy swelling of the cells, and followed by the appearance of granules which soon develop into fat globules. Eventually, these cells break up into detritus.

Another feature, seen oftener after repeated small doses, is the proliferation of interstitial connective tissue of the stomach, liver and kidneys which finally induces a typical cirrhosis of these organs. It appears to be secondary to necrosis of the parenchymatous cells.

Grossly, the liver is enlarged, has a lemon yellow tint and feels greasy and soft. Small hemorrhages may be seen on the surface and on cut sections. Microscopically, there is extreme fatty degeneration of hepatic cells with accumulation of fat in the Kupffer cells.[16b] Mallory presented a classic description of cirrhosis experimentally produced with phosphorus and its possible relation to cirrhosis in man.[22] However, even though this condition resembles human cirrhosis, with granules and hyaline networks in acidophilic hepatic cells, its production in rabbits and guinea pigs requires months of daily doses of yellow phosphorus. LaDue and associates followed a patient with acute phosphorus poisoning with repeated biopsies of the liver.[3] They observed focal necrosis, fatty metamorphosis and parenchymatous degeneration, with acute inflammation of the portal canals in the early phase of the illness. Later phases were characterized by a proliferation of periportal connective tissue, histologically compatible with early portal cirrhosis.

The nervous system seems to be especially vulnerable to phosphorus. The inferior olivary bodies and the lipophilic cells of the nervous system are involved early with fatty degeneration.[18] Spielmeyer noted the occurrence of purpura of the brain in phosphorus poisoning, which he attributed to changes in the coagulability of the blood.[23] Hammer reported on an adult who revealed pronounced fatty degeneration of the cortex of the brain.[24] The distribution of this fatty infiltrate in the various parts of the nervous parenchyma is of special interest. In his excellent review of the subject, Wertham pointed out that those cells

22. Mallory, F. B.: Phosphorus and Alcoholic Cirrhosis, Am. J. Path. **9**:557, 1933.

23. Spielmeyer, W.: Die Diagnose "Entzündung" bei Erkrankungen des Zentralnervensystems, Ztschr. f. d. ges. Neurol. u. Psychiat. **25**:543, 1914.

24. Hammer, H.: Ein Fall von Phosphorvergiftung mit selten rasch letalem Ausgange, Prag. med. Wchnschr. **14**:79, 1889.

which normally contain much lipofuscin, and which Obersteiner therefore called lipophilic, are those most affected.[1n] The lipophobic cells of the area striata and the Purkinje cells, on the other hand, do not participate in this pathologic fatty infiltration.

METABOLIC CHANGES

The changes in metabolism occurring as the result of acute phosphorus poisoning are among the most interesting features of this disorder. These changes consist of increased destruction of tissue with disturbances of synthesis, oxidation and dissociation, increased but incomplete nitrogen metabolism, interference with glycogen deposition, increased excretion of lactic acid and ammonia and deposition of fat in the liver. The mechanisms of these changes are not completely understood, but they appear to involve interference with certain enzymatic systems, primarily those involved in carbohydrate metabolism.

Many observations, especially during the early part of this century, were made on the disturbance in carbohydrate metabolism occurring in acute phosphorus poisoning. Althausen and Thoenes reviewed many of the carbohydrate metabolic and hepatic changes in rabbits.[25] The more important of these disturbances are briefly enumerated in the following paragraphs:

1. The blood sugar is temporarily increased, but after large doses this increase is followed by a severe hypoglycemia,[26] due in part to the severe damage to the liver. Dextrose tolerance tests reveal an abnormally high rise in venous blood sugar concentrations, with the maximum concentration being attained within an hour in most cases. The blood sugar usually falls rapidly and returns to its original level within two or three hours. However, in cases of extreme hepatic insufficiency, the hyperglycemia may be more prolonged. The arterial-venous difference is usually normal or in some instances may even be increased.[27a]

2. The diastase of the serum is greatly increased, with a decrease in the lipase and no changes in protease. These results also occur after excision of the pancreas and are presumably due to the action of the liver.[28]

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25. Althausen, T. L., and Thoenes, E.: Influence on Carbohydrate Metabolism of Experimentally Induced Hepatic Changes: Phosphorus Poisoning, Arch. Int. Med. **50**:58 (July) 1932.

26. Ivanevic, 1927, cited by Sollmann,[12] p. 812.

27. (*a*) Cantarow, A., and Trumper, M.: Clinical Biochemistry, ed. 3, Philadelphia, W. B. Saunders Company, 1945, pp. 41, (*b*) 414, (*c*) 51, (*d*) 158, (*e*) 137 and (*f*) 418.

28. Falkenhausen, 1938, cited by Sollmann,[12] p. 812.

3. Phosphorus causes the disappearance of glycogen from the liver. Since this is not due to increased glycogenolysis, it probably represents inhibited glycogen synthesis especially from noncarbohydrate sources.[29] This would explain the prevention of epinephrine glycosuria by phosphorus and the noncombustion of lactic acid.[27b]

4. According to Von Fürth, lactic acid appears in the urine only when rabbits poisoned with phosphorus are fed an excess of sugar.[30] Dextrose is not converted into glycogen, probably explaining the occurrence of glycosuria when carbohydrate is fed.[31]

5. The tolerance for galactose and levulose is lowered.[32]

6. As early as 1911, Frank and Isaac [29b] were of the opinion that the interference with glycogen synthesis is the primary action of phosphorus, and they attributed the increase of destruction of protein to the necessity of making up for the lessened supply of energy material. Hence, the increase in nitrogen excretion may be due primarily to the carbohydrate disturbance. Accordingly, in 1914, Rettig reported that a diet rich in carbohydrate prevents the increased protein catabolism and fatty changes in phosphorus poisoning.[33]

7. Ray, McDermott and Lusk made the interesting observation that in dogs which had been rendered glycosuric by phlorhizin, phosphorus does not increase the nitrogen excretion, which again indicated to them that the nitrogen excretion is not due to direct destruction of the protoplasm, but is in some way connected with the disturbed carbohydrate metabolism.[34]

Nitrogen and protein metabolism are greatly increased in acute phosphorus poisoning. Among the phenomena described are the following:

1. The urinary nitrogen may rise by 300 per cent with all the nitrogenous metabolites being involved, especially ammonia. Urea is less involved, since hepatocellular damage is so heavy, and consequently the total nitrogen: urea ratio of the blood rises.[29a]

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29. (*a*) Desqueyroux, J.: Sur les troubles des échanges azotés dans l'intoxication phosphorée aiguë expérimentale, Compt. rend. Soc. de biol. **86**:143, 1922. (*b*) Frank, E., and Isaac, S.: Beiträge zur Theorie experimenteller Diabetesformen (im Anschluss an Untersuchungen mit Hilfe der Phosphorvergiftung), Arch. f. exper. Path. u. Pharmakol. **64**:293, 1911.

30. Von Fürth, O.: Ueber die Beziehungen der Milchsäure zum Kohlehydratstoffwechsel: I. Ueber das Auftreten der Milchsäure im Kaninchenhain bei der Phosphorvergiftung, Biochem. Ztschr. **44**:131, 1914.

31. Neubauer, O.: Levulose, Arch. f. exper. Path. u. Pharmakol. **61**:174, 1909.

32. (*a*) Marshall, E. K.: Phosphorus and Chloroform, J. Exper. Med. **22**:333, 1915. (*b*) Caytarow and Trumper.[27c]

33. Rettig, H.: Zur Frage des toxogenen Eiweisszerfalls bei der Phosphorvergiftung, Arch. f. exper. Path. u. Pharmakol. **76**:345, 1914.

34. Ray, McDermott and Lusk, cited by Sollmann,[12] p. 812.

2. There is an increase in nonprotein introgen and blood amino acids in dogs poisoned with phosphorus and a terminal acidosis.[32a] This has been also observed in human beings, with amino acids ranging from 10 to 30 mg. per hundred cubic centimeters owing to hepatic damage.[27a]

3. Amino acids, especially leucine, tyrosine and cystine, appear in the urine along with peptone-like substances, which were first noted in phosphorus poisoning in 1869.[35]

Most observers [36] expressed the opinion that the increased fat in the liver, heart and other organs represents a process of fatty infiltration, although changes in the depot fat have also been noted. These changes consisted of desaturation and an increased iodine number.[32a] Among other changes in fat metabolism which have been observed are hypocholesteremia, with a diminished proportion of cholesterol esters due mostly to hepatocellular damage,[37] and lipuria.[27e]

It is obvious from the foregoing discussion that there is clinically and pathologically profound hepatocellular damage and functional derangement briefly manifested by the following signs: disappearance of glycogen with subsequent fatty infiltration; incomplete combustion of lactic acid; diminished urea formation with increased excretion of ammonia; increased protein destruction with incomplete deaminization of certain amino acids; mechanical interference with bile excretion and production of jaundice, and decreased fibrinogen which, together with the toxic changes in the capillaries and a possible diminished antithrombin content of the blood noted by Denny and Minot,[38] allows for a hemorrhagic diathesis that contributes to the high mortality in this condition.

METHODS FOR DETECTION OF PHOSPHORUS

In acute phosphorus poisoning the gastrointestinal contents are of prime importance from an analytic standpoint. Phosphorus may be detected in the unoxidized form for several days, and it has been found in the body after burial for a month. The material is distilled in a dark room, screening off the light from the Bunsen burner. If white phosphorus is present, a luminescent ring will be noticed during the distillation in the upper part of the water-cooled condenser.

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35. Schultzen, O., and Riess, L.: Phosphorus, Chem. Centralbl., 1869, p. 680.

36. Lebedeff, A.: Woraus bildet sich das Fett in Fällen der acuten Fettbildung? Arch. f. d. ges. Physiol. **31**:11, 1883. Foulerton, A. G. R.: Liver Poisons, J. Path. & Bact. **24**:257, 1921. Athanasiu, J.: Die Erzeugung von Fett im thierischen Körper unter dem Einfluss von Phosphor, Arch. f. d. ges. Physiol. **74**:511, 1899.

37. Thannhauser, S. J., and Schafer, H.: Ueber die Beziehungen des Gleichgewichtes Cholesterin und Cholesterinester im Blut und Serum zur Leberfunction, Klin. Wchnschr. **5**:252, 1926. Cantarow and Trumper.[27d]

38. Denny, G. P., and Minot, G.: The Origin of Antithrombin, Am. J. Physiol. **35**:233, 1914.

Phosphorus may also be detected by the Mitscherlich test.[14] A distillate of the organ to be tested is strongly acidified with concentrated nitric acid and then evaporated to dryness on a water bath. This converts phosphorus to phosphoric acid, which can then be identified by the addition of ammonium phosphomolybdate.

TREATMENT

In treatment of a patient with acute phosphorus poisoning, it is wise for the examiner to put on a covering gown down to the wrists, as glabrous skin may be burned painfully by flecks of vomitus or feces. Treatment of the patient, which must be started as soon as the diagnosis is suspected, should include the following procedures:

1. External heat should be applied.

2. The stomach is lavaged, using a large pliable rubber suction tube. Cupric sulfate, 1 Gm. to 1 pint (500 cc.) of water, should be used in copious amounts. This acts as both an emetic and an antidote which envelops the phosphorus particles, leading to the formation of the insoluble copper phosphide. Two per cent hydrogen peroxide solution or 1 : 1,000 potassium permanganate solution may be used as lavages, both forming harmless oxidation products. Sodium thiosulfate and sodium iodide may be used if there is any suspicion of arsenic or thallium poisoning.

3. Purges, such as magnesium sulfate, should be left in the stomach following the lavage. Phosphorus has been discovered in the stools for three days after its ingestion.[6a]

4. Fats and oils are to be avoided. These tend to dissolve the poison and promote its absorption. However, Atkinson [39] showed that some laboratory animals could be saved from acute phosphorus poisoning by administration of liquid petrolatum in large amounts. The phosphorus is soluble in this and hence is not absorbed. For this reason it is recommended that 100 to 200 cc. of liquid petrolatum be introduced into the stomach.

5. The acute hepatic insufficiency should be treated with vitamins, especially those of the B complex and vitamin K, with dextrose intravenously and a daily intake of a high carbohydrate, high protein, low fat, liquid diet, provided the patient is conscious and can swallow.

6. Calcium lactate or gluconate, 1 Gm. three times a day, may be administered.

7. Penicillin should be given in large doses as prophylaxis.

8. Catheterization of the bladder in order to follow urinary output and sediment and to prevent distention of the bladder is necessary, particularly in the unconscious patient.

39. Atkinson, H.: Phosphorus Poisoning, J. Lab. & Clin. Med. **7**:148, 1921.

9. BAL should be administered when there is any question of arsenic poisoning.

10. Isotonic sodium chloride and sodium lactate solutions are given parenterally as indicated to treat the chemical imbalances of shock, acidosis or dehydration.

11. Blood transfusions should be given as indicated.

12. Local phosphorus burns should be treated with 1 per cent cupric sulfate solution and bland topical substances.

SUMMARY AND CONCLUSIONS

Acute phosphorus poisoning constitutes a serious medical and public health problem, as indicated by its high mortality and the easy accessibility of substances, especially rat poisons, which contain yellow phosphorus.

A brief review of the historic aspects of phosphorus poisoning and a description of the properties and preparations of phosphorus are presented.

The three clinical stages of acute phosphorus poisoning are described, with stress on the importance of the garlicky odor to the breath and the presence of luminescent vomitus.

Data on 16 patients with acute phosphorus poisoning admitted to the Boston City Hospital are presented and the clinical course of 3 described in detail.

The pathologic changes taking place in acute phosphorus poisoning and the changes occurring in the metabolism of carbohydrates, fats and proteins are described.

The treatment of acute phosphorus poisoning is presented.

Dr. Ralph Myerson, Veterans Hospital, Wilmington, Delaware.

INFECTIOUS MONONUCLEOSIS WITH NEUROLOGIC COMPLICATIONS

Report of a Fatal Case

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INFECTIOUS mononucleosis, until recently, has been regarded as a mild disease with few complications and with a uniformly favorable outcome. Glanzmann,[1] in 1930, stated in his monograph that the prognosis in infectious mononucleosis, as in German measles, is absolutely favorable. In the opinion of Contratto[2] (1944) infectious mononucleosis is attended with no more complications than an ordinary infection of the respiratory tract. However, there are several forms of serious complications in this disease (hepatitis, thrombocytopenia, myocarditis, spontaneous rupture of the spleen and involvement of the central and peripheral nervous system), with instances of fatal outcome from the latter three. Multiple serious complications may occur in the same patient.

Electrocardiographic changes have been reported by several authors,[3] with death in Jersild's [3a] case. Microscopic evidence of focal myocarditis and of involvement of the central nervous system was found in a recently discharged convalescent patient who had died in an airplane crash on a solo flight (Allen and Kellner[4]).

From the Pathologic Laboratories and from the Communicable Disease Service of the Willard Parker Hospital.

1. Glanzmann, E.: Das lymphaemoide Drüsenfieber, in Abhandlungen aus der Kinderheilkunde und ihren Grenzgebieten, Beihefte zum Jahrbuch für Kinderheilkunde, 1930, no. 25.

2. Contratto, A. W.: Infectious Mononucleosis: Study of One Hundred and Ninety-Six Cases, Arch. Int. Med. **73**:449 (June) 1944.

3. (*a*) Jersild, T.: Mononucleosis infectiosa med letald forløb, Nord. med. (Hospitalstid.) **14**:1705 (June 6) 1942. (*b*) Logue, R. B., and Hanson, J. F.: Heart Block: A Study of One Hundred Cases with Prolonged P-R Interval, Am. J. M. Sc. **207**:765 (June) 1944. (*c*) Candel, S., and Wheelock, M. C.: Acute Non-Specific Myocarditis, Ann. Int. Med. **23**:309 (Sept.) 1945. (*d*) Lyon, E.: Acute Myocarditis as a Sequel to Infectious Mononucleosis (Contribution to Problem of Virus Myocarditis), Acta med. orient. **5**:228 (July) 1946. (*e*) Jaffe, H. L.; Field, L. E., and Master, A. M.: The Electrocardiogram in Infectious Mononucleosis, New York State J. Med. **48**:1382 (June 15) 1948.

4. Allen, F. H., and Kellner, A.: Infectious Mononucleosis: An Autopsy Report, Am. J. Path. **23**:463 (May) 1947.

Splenomegaly, with spontaneous rupture of the spleen, was reported in 13 cases,[5] with a fatal outcome in 5 cases and with successful surgical removal of the spleen in others. In the case of Vaughan, Regan and Terplan [5g] neurologic manifestations were present in a patient with rupture of the spleen.

Instances of transitory damage of the central nervous system are fairly numerous in the literature. In most cases the symptomatology was indicative of involvement of the cerebral meninges [6] or of the brain, with or without meningitis.[7] In some of these cases there was transient involvement of the cranial nerves, with resulting optic neuritis, oculomotor disturbances and facial paralysis. A persistent anosmia (of two months' duration at the time of the report) was observed by Marchal

5. (*a*) King, R. B.: Spontaneous Rupture of Spleen in Infectious Mononucleosis, New England J. Med. **224**:1058 (June 19) 1941. (*b*) Darley, W.; Black, W. C.; Smith, C., and Good, F. A.: Spontaneous Splenic Rupture in Infectious Mononucleosis: Case and Pathologic Report, Am. J. M. Sc. **208**:381 (Sept.) 1944. (*c*) Ziegler, E. E.: Infectious Mononucleosis: Report of a Fatal Case with Autopsy, Arch. Path. **37**:196 (March) 1944. (*d*) Davis, J. S.; McFee, W.; Wright, M., and Allyn, R.: Rupture of Spleen in Infectious Mononucleosis, Lancet **2**:72 (July 21) 1945. (*e*) Milne, J.: Infectious Mononucleosis, New England J. Med. **233**:727 (Dec. 13) 1945. (*f*) Smith, E. B., and Custer, R. P.: Rupture of the Spleen in Infectious Mononucleosis: A Clinico-Pathologic Report of Seven Cases, Blood **1**:317 (July) 1946. (*g*) Vaughan, S. L.; Regan, J. S., and Terplan, K.: Infectious Mononucleosis Complicated by Spontaneous Rupture of the Spleen and Central Nervous System Involvement, ibid. **1**:334 (July) 1946.

6. (*a*) Johansen, A. H.: Serous Meningitis and Infectious Mononucleosis, Acta med. Scandinav. **76**:269, 1931. (*b*) Thelander, H. E., and Shaw, E. B.: Infectious Mononucleosis, with a Special Reference to Cerebral Complications, Am. J. Dis. Child. **61**:1131 (June) 1941. (*c*) Tidy, H.: Relationship of Benign Lymphocytic Meningitis and Glandular Fever, Lancet **2**:819 (Dec. 7) 1946.

7. (*a*) Epstein, S. H., and Dameshek, W.: Involvement of Central Nervous System in a Case of Glandular Fever, New England J. Med. **205**:1238 (Dec. 24) 1931. (*b*) Marchal, G.; Bargeton, and Mahoudeau: Angine à monocytes, avec biopsie, Sang **7**:431, 1933. (*c*) Fledelius, M.: Augenmuskellähmung als Komplikation der mononucleosis infectiosa, Acta ophth. **13**:150, 1935. (*d*) Sucher, A., and Schwartz, E.: Lymphatische Reaction und Encephalomeningitis, Wien. klin. Wchnschr. **49**:1417 (Nov. 20) 1946. (*e*) Gsell, O.: Meningitis serosa bei Pfeifferschem Drüsenfieber (Mononucleosis infectiosa), Deutsche med. Wchnschr. **63**: 1759 (Nov. 19) 1937. (*f*) Davidsohn, I.: Serologic Diagnosis of Infectious Mononucleosis, J. A. M. A. **108**:289 (Jan. 23) 1937. (*g*) Schmidt, V., and Nyfeldt, A.: Ueber Mononucleosis infectiosa und Meningoencephalitis, Acta otolaryng. **26**:680, 1938. (*h*) Thomsen, S., and Vimtrup, B.: Six Fatal Cases of Infectious Mononucleosis Complicated by Central Respiratory Paralysis, Nord. med. (Hospitalstid.) **4**:3295 (Nov. 11) 1939. (*i*) Marshall, E. A.: Infectious Mononucleosis, Am. J. Clin. Path. **9**:298 (May) 1939. (*j*) Landes, R.; Reich, J. P., and Perlow, S.: Central Nervous System Manifestations of Infectious Mononucleosis, J. A. M. A. **116**:2482 (May 31) 1941. (*k*) Solomons, B.: Infective Mononucleosis: Some Meningeal Features, J. Roy. Nav. M. Serv. **31**: 178 (July) 1945.

and others.[7b] Fatal cases with central paralysis of the respiratory tract were reported by Thomsen and Vimtrup.[7h]

Involvement of peripheral nerves, spinal roots and spinal cord occurs less frequently. Paralysis of the long thoracic nerve was observed in 2 cases. It was transient in Richardson's case [8] and permanent in Saksena's patient.[9] Cases of Guillain-Barré syndrome have been reported by Hiller and Fox,[10] by Coogan, Martinson and Mathews [11] and by Ricker, Blumberg, Peters and Widerman,[12] with fatal outcome in 2 cases of the latter authors. Cases of encephalomyelitis with a clinical picture resembling that of poliomyelitis have been reported by Zohman and Silverman,[13] by Geliebter [14] and by Slade,[15] with residual damage in 3 of 4 cases.

Microscopic observations in the central nervous system have been described in three papers. Death clinically attributable to respiratory failure of central origin was reported by Thomsen and Vimtrup [7h] in 4 of their 6 fatal cases. The central nervous system was examined microscopically in 1 case and showed "degenerative changes in the cells of the respiratory center" in the medulla. In a case of traumatic death of a convalescent patient who had had no neurologic manifestations, Allen and Kellner [4] found perivascular cuffing in the cerebral cortex. In 2 cases of Guillain-Barré syndrome, Ricker, Blumberg, Peters and Widerman [12] described small perivascular hemorrhages in the brain and cord, degenerative cellular changes in the cerebellum and cord and mononuclear infiltration of spinal roots and nerves and of some cranial nerves.

The involvement of the central nervous system in several cases developed before the enlargement of the lymphoid organs and presented considerable diagnostic difficulties. In the case reported here some of

8. Richardson, J. S.: Serratus Magnus Palsy, Lancet **1**:618 (May 23) 1942.

9. Saksena, H. C.: Paralysis of the Serratus Anterior Following Glandular Fever, Brit. M. J. **2**:267 (Aug. 28) 1943.

10. Hiller, R. I., and Fox, M. J.: Infectious Neuronitis Associated with Infectious Mononucleosis, Marquette M. Rev. **7**:152 (Feb.) 1943.

11. Coogan, T. J.; Martinson, D. L., and Mathews, W. H.: Neurological Symptoms of Infectious Mononucleosis, Illinois M. J. **87**:296 (June) 1945.

12. Ricker, W.; Blumberg, A.; Peters, C. H., and Widerman, A.: The Association of the Guillain–Barré Syndrome with Infectious Mononucleosis, with a Report of Two Fatal Cases, Blood **2**:217 (May) 1947.

13. Zohman, B. L., and Silverman, E. G.: Infectious Mononucleosis and Encephalomyelitis, Ann. Int. Med. **16**:1233 (June) 1942.

14. Geliebter, S.: Acute Infectious Mononucleosis Complicated by Encephalomyelitis, Lancet **2**:753 (Nov. 23) 1946.

15. Slade, J. de R.: Involvement of the Central Nervous System in Infectious Mononucleosis: A Report of Two Cases, New England J. Med. **234**:753 (June 6) 1946.

the neurologic signs appeared early in the disease. After the diagnosis of infectious mononucleosis had been made, a new series of signs developed, producing a clinical picture resembling that of poliomyelitis.

REPORT OF A CASE

The patient was a white woman 19 years old, an office worker. Her illness began on Oct. 13, 1947, with malaise, feeling of fatigue, backache and weakness of the legs. On the following day she had a sore throat and a temperature of 102 F. On October 15 photophobia, double vision and swelling of the eyelids developed. On the following day she was admitted to the Pearl River Hospital to the service of Dr. Thomas Cassara and was given sulfonamide and penicillin therapy. On October 17 the patient was toxic and had generalized lymphadenopathy and a palpable spleen. Her white blood cell count was 9,000, with 40 per cent lymphocytes.[16] On the following day sluggish reflexes were noted. The white blood cell count showed a slight increase in the number of lymphocytes (9,000 cells, with 45 per cent lymphocytes). On October 19 she had a severe headache. The eyegrounds were normal. The throat was red, without a membrane. On October 20 she had a stiff neck. The spinal fluid was under increased pressure and contained 50 cells, with normal sugar content and no increase in protein. Nose and throat cultures were negative for Corynebacterium diphtheriae. The heterophile antibody test gave a positive reaction in a dilution of 1:448. On October 21 the patient had positive Kernig and Brudzinski signs, was unable to move her legs and had difficulty in swallowing. There was a membrane on the tonsils. The reaction to the heterophile antibody test was positive in 1:1,792 dilution. The patient was transferred to the Willard Parker Hospital on October 22 as having bulbar poliomyelitis.

On admission, the patient was stuporous and could not swallow. Her temperature was 98.6 F. A membrane was present on both tonsils. There was generalized lymphadenopathy, but the spleen was not palpable. There was slight nuchal rigidity. The corneal reflexes were sluggish. Only abdominal reflexes could be elicited. The spinal fluid was clear, and there was no increase in pressure and no cells. The Pandy test gave a negative reaction. The heart was normal. The lungs showed diminished breath sounds. After a negative reaction to a skin sensitivity test, diphtheria antitoxin was given (50,000 units intravenously and 25,000 units intramuscularly). Oxygen and suction were used continuously and she was given penicillin and plasma. Her blood count showed 21,000 white cells, with 49 per cent lymphocytes, of which 11 were abnormal.

Two and one-half hours after admission the patient suddenly became cyanotic, with a rapid and thready pulse. She did not respond to therapy and died ten minutes later.

The total duration of illness was nine days.

Subsequent Laboratory Findings.—Cultures from the nose and throat showed the presence of Streptococcus hemolyticus and Staphylococcus aureus but no C. diphtheriae. The blood count, rechecked with peroxidase stain on a 300 cell count, showed 2.6 per cent metamyelocytes, 22.3 per cent band forms, 17 per cent segmented neutrophils, 40 per cent normal lymphocytes, 11.5 per cent abnormal lymphocytes and 6.5 per cent monocytes. The reaction to the heterophile antibody test (performed by Dr. Annis E. Thomson, of the Research

16. No detailed differentiation of cells has been done, and no smears were available for additional study.

Laboratories of the New York City Health Department) was positive in a dilution of 1:14,336 with the unabsorbed serum and 1:7,168 after absorption with the guinea pig kidney. The agglutinins were absorbed by boiled beef red blood cells. The Kline test gave a negative reaction. Blood culture was sterile. Chemical analysis of the blood (post mortem, on a specimen of heart's blood) showed a non-protein nitrogen content of 51.7 mg. and a cholesterol content of 147 mg. per hundred cubic centimeters. Virus studies of the lymph nodes and spleen were

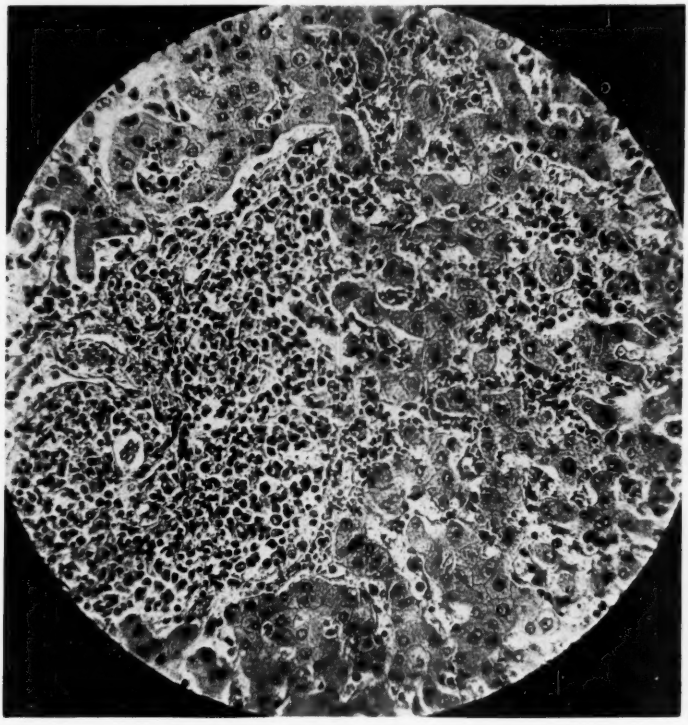

Fig. 1.—Liver. Collections of large lymphoid cells are present in the portal areas and in the sinusoids. Hematoxylin and eosin stain; × 240.

made by Dr. George K. Hirst, of the Public Health Research Institute, and the results were negative.

Gross Findings at Necropsy.—The necropsy was performed four hours after death. The body was well developed and well nourished. The skin was pale and clear. The pupils were equal and in mid-dilatation. Several enlarged lymph nodes could be felt in the left posterior cervical region, a few in the axillas and one or two in each inguinal region. The liver was within the costal margin, but the percussion sound was flat not only over the right side of the hypochondrium

but over the epigastrium and the left side of the hypochondrium as well. The spleen could not be felt. The mesenteric lymph nodes were congested but not large, except for a few nodes at the root of the mesentery, near the head of the pancreas. The intestine showed nothing remarkable. The appendix was 12 cm. long and retrocecal but otherwise normal. The heart weighed 300 Gm. but appeared large because of dilatation of the right ventricle, which was filled with liquid blood. There was no innominate artery. The right carotid began directly from the aortic arch, and the right subclavian began from the descending aorta,

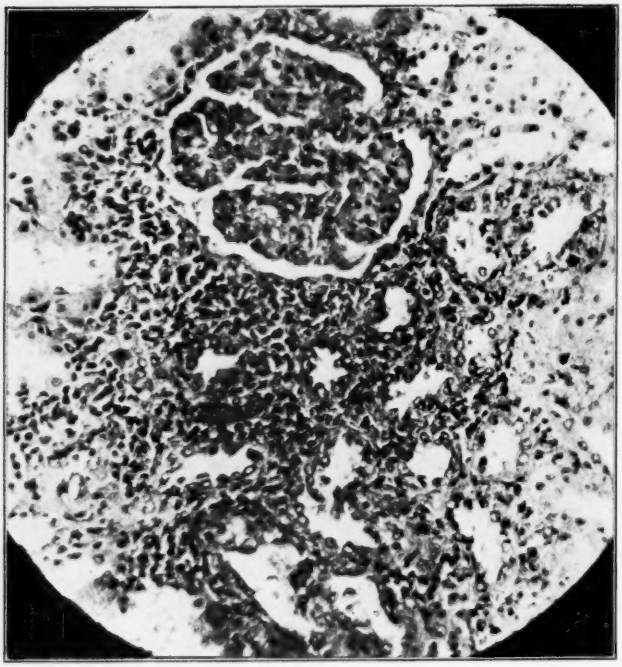

Fig. 2.—Kidney. Collections of large lymphoid cells are seen in the interstitial tissue. Hematoxylin and eosin stain; × 240.

below the left subclavian, and assumed a retroesophageal course across the vertebral column toward the area of the right scalenus.

Thymus: The thymus was flat and large, weighed 18 Gm. and contained little fat.

Lungs: Both lungs were free, and each consisted of three lobes. The upper and middle lobes were air-holding, except for a small depressed red area in the upper lobe of the right lung. The posterior aspects of both lower lobes showed depressed red areas; on section these areas were red and shiny, with tissue sinking

in water. The bronchi contained some pinkish fluid. There were no enlarged lymph nodes in the hilar regions.

Trachea and Large Bronchi: These contained a small amount of pink mucoid material.

Larynx: The larynx was normal, and its mucosa was pale.

Fauces: The tonsils were greatly enlarged and only moderately congested, presented a granular surface and were cryptic, with thick greenish pus filling the crypts. A grayish area was present on the upper pole of the right tonsil. The soft palate and the posterior pharyngeal wall were congested. The lymphoid tissue at the base of the tongue was hyperplastic and moderately congested.

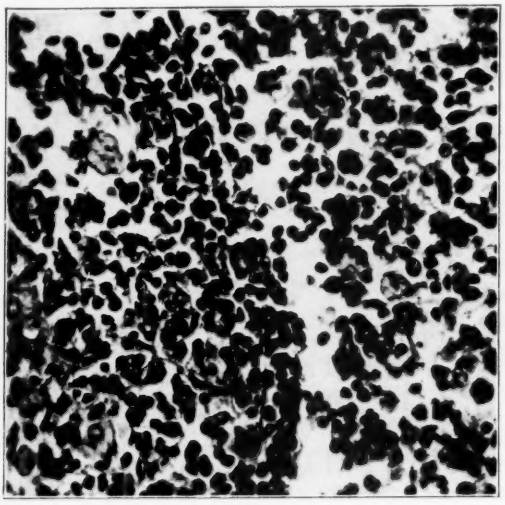

Fig. 3.—Tonsil. The lymphoid follicle (left) contains small lymphocytes and vacuolated reticulum cells. Large lymphocytes are present in the edematous surrounding tissue. Hematoxylin and eosin stain; × 480.

Lymph Nodes: Deep cervical lymph nodes were numerous and were arranged in chains in front of the left carotid and outside the right carotid, where they were embedded in fat tissue. Some nodes were pale and others hemorrhagic. The larger nodes were 1.5 cm. long and 1 cm. in diameter. Deep axillary lymph nodes were embedded in fat and were more numerous on the left axilla than on the right. They were pale and were from 1 to 2 cm. long and from 0.5 to 1 cm. in diameter.

Liver: The liver filled the epigastrium and the left hypochondrium, covering the entire stomach. It weighed, however, only 1,900 Gm. and was smooth and moderately congested. On section the design of the capillaries was indistinct. The parenchyma bulged slightly and was markedly friable.

Gallbladder and Spleen: The gallbladder emptied readily. The spleen weighed 560 Gm. and was situated behind the stomach. There was a long rent

in the capsule, with the pulp protruding but not torn. As there was no bleeding, it seemed probable that the capsule was torn after death, while the body was being moved from the ward to the mortuary. The capsule was exceptionally thin and peeled readily from the surface. The splenic pulp was extremely friable and the color of red vulcanized rubber sponge, with dark red blood oozing freely on slightest pressure. A few irregular grayish areas about 3 mm. in diameter could be seen beneath the capsule, but on section they corresponded to small pale areas in the otherwise congested and extremely hyperplastic pulp. The lymphoid follicles could not be identified.

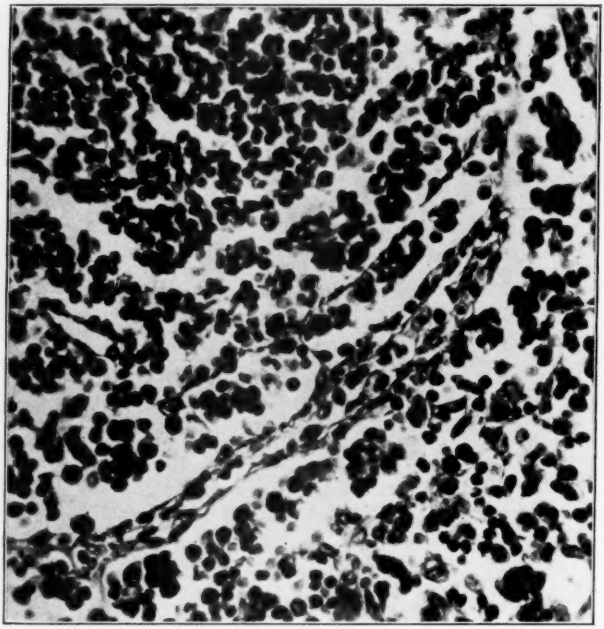

Fig. 4.—Lymph node. The lymphoid follicle (upper left corner) consists of small lymphocytes. Large, dark lymphocytes and pale reticulum cells are present in the sinuses. Hematoxylin and eosin stain; × 480.

Pancreas: The pancreas weighed 100 Gm.

Adrenal Glands: The adrenal glands weighed 12 and 15 Gm. and appeared to be grossly normal.

Kidneys: The kidneys weighed 210 and 220 Gm. The capsules stripped readily. The pyramids were dark red, and the cortex was wide and markedly congested and bulged slightly.

Urinary Bladder, Uterus and Adnexa: These appeared normal.

Gastrointestinal Canal: The gastric mucosa was pale and folded. The duodenum was notably congested, but the mucosa of the rest of the intestine was only moderately injected. A few Peyer patches were slightly elevated, and the solitary follicles of the large intestine were pinhead sized and appeared white on the pinkish mucosa.

Brain and Spinal Cord: The brain weighed 1,100 Gm. The meninges were moderately edematous and congested. The brain was not edematous and on section showed only moderate congestion. The medulla showed nothing remarkable

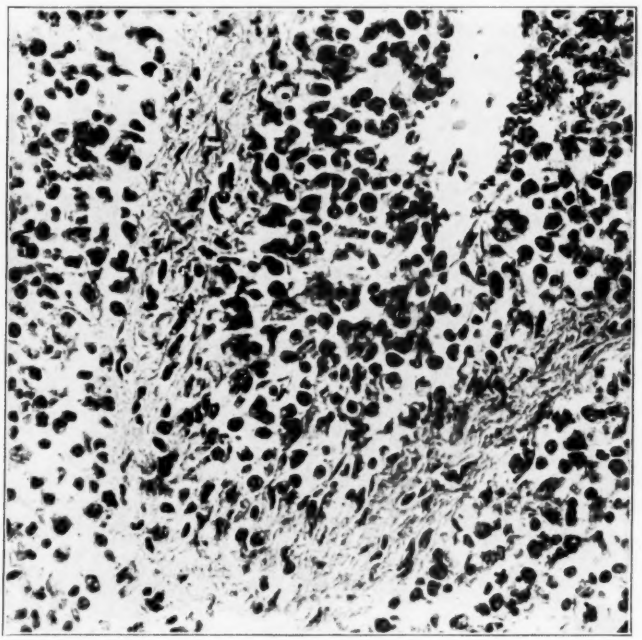

Fig. 5.—Spleen. Large lymphocytes infiltrate the intima of a trabecular vein. Similar cells are present in the splenic pulp around the vein. Hematoxylin and eosin stain; × 480.

grossly. The gray matter of the cord from the cervical through the lumbar region appeared diffusely hemorrhagic. The sacral cord was free of hemorrhages.

Microscopic Changes.—The heart showed moderate edema of the myocardium and loss of striation in a few fibers.

Lungs: Areas of atelectasis were present in both lungs. Edema fluid and blood were present in some alveoli. A few scattered alveoli of the left lung contained some polymorphonuclear cells. The walls of several alveoli of the right lung were somewhat thickened and contained an increased number of mononuclear cells. The bronchial epithelium was partly desquamated, and the bronchial lumen

contained some red cells and polymorphonuclear cells. The mucosa was infiltrated with small lymphocytes. Several small loose groups of lymphocytes were present in the pleura and in the interlobular septums, but there was no interstitial pneumonitis.

Liver (fig. 1): The portal areas were heavily infiltrated with mononuclear cells, about 25 per cent of which were normal, small lymphocytes, while the rest were larger cells with large, pale nuclei. Smaller collections of similar cells were present in the sinusoids of some lobules.

Adrenal Glands: A few small collections of various-sized mononuclear cells were present in the cortex and medulla.

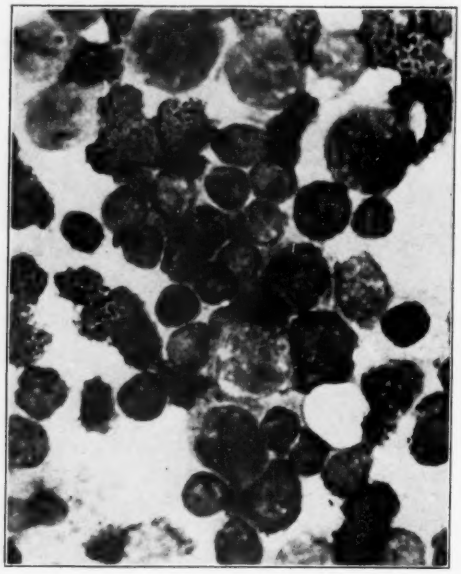

Fig. 6.—Smear from the splenic pulp, containing large and small lymphocytes and crenated red blood cells. The large lymphocytes are identical with, and more numerous than, the "abnormal lymphocytes" of the peripheral blood. MacNeal's tetrachrome stain; oil immersion; × 1,060.

Kidneys: Large collections of various-sized mononuclear cells were present near the blood vessels at the border of the cortex and the pyramids, and several smaller collections were found in the cortex, around some glomeruli, between the tubules and beneath the capsule (fig. 2).

Lymphoid Organs: Tonsil. The surface was largely devoid of epithelium or covered by a single row of squamous cells. In several places a few strands of fibrin were loosely attached to the denuded surface, forming a thin membrane. The crypts contained necrotic squamae and some polymorphonuclear cells. The lymphoid follicles consisted of small lymphocytes, some large lymphoid cells and a small number of large, pale polyhedral or elongated reticulum cells containing

numerous vacuoles (fig. 3). The follicles were rather far apart, and the pulp between them was edematous and contained various-shaped large mononuclear cells and only a small number of normal lymphocytes. Most of the large lymphoid cells had a small amount of purplish cytoplasm and a large round nucleus, often with a pink nucleolus. Occasional cells had two nuclei. Mitosis was seen in only a few cells. Several medium-sized multinucleated cells with pink cytoplasm and scattered elongated nuclei were encountered. The peritonsillar tissues were only slightly infiltrated with normal small lymphocytes.

Tongue. The lymphoid tissue was abundant and presented a picture similar to that of the tonsils. The epithelium was thick, and the lingual musculature was not infiltrated with lymphocytes.

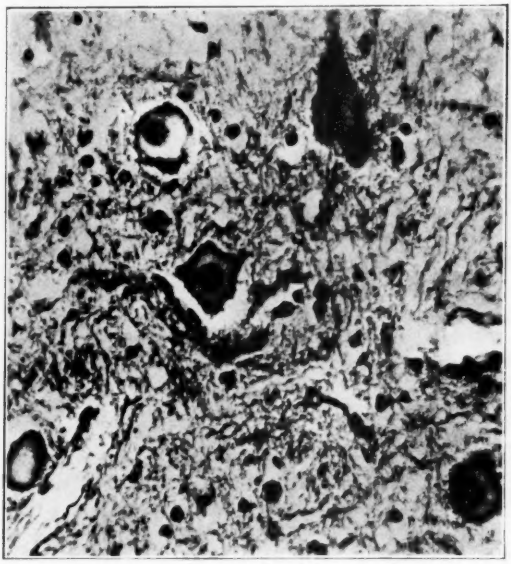

Fig. 7.—Nucleus of the fourth cranial nerve. The cytoplasm of four cells is hydropic, but the cells are small. The nuclei are compact and dark. Hematoxylin and eosin stain; × 480.

Cervical, axillary and peripancreatic lymph nodes. The follicles were compact and consisted of small, normal lymphocytes and contained no vacuolated cells. In the loose surrounding tissue and the sinuses, in addition to small lymphocytes, a number of large "abnormal" lymphocytes and many cells with abundant pink cytoplasm and small nuclei were present (fig. 4). On impression smears, the large lymphocytes had the same structure as the "abnormal" lymphocytes of the peripheral blood. Other lymph nodes and the lymphoid tissue of the small intestine, appendix and colon presented the usual appearance and contained no abnormal cells.

Thymus. This was unusually well preserved for an adult and consisted of normal lymphocytes and some degenerated Hassall's corpuscles.

Spleen. The pulp consisted of poorly limited pools of blood which spread into the remnants of splenic cords and into the Malpighian bodies, which contained only a few small lymphocytes and numerous large lymphoid elements identical with those of the tonsillar stroma. The same cells were present in the remnants of the splenic cords, in the pulp along the trabeculae and in the intima of the trabecular veins (fig. 5). Impression smears from the splenic pulp showed that the large cells were identical with the "abnormal" lymphocytes of the peripheral blood (fig. 6). They were far more abundant in the smears from the spleen than in those from the axillary lymph nodes.

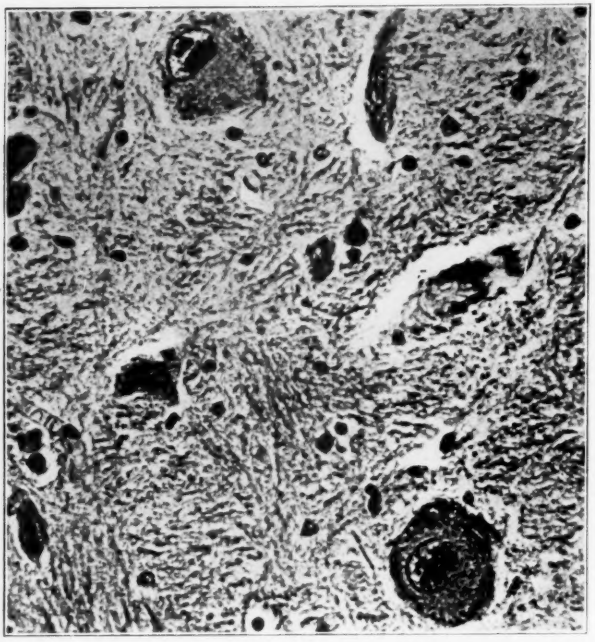

Fig. 8.—Reticular nucleus of the medulla. The Nissl substance of two cells is on the periphery. The chromatin of the nuclei is rolled up into an elongated body clinging to the nuclear membrane. The nucleolus is preserved. Cresyl violet stain; × 480.

Thyroid, Parathyroids, Pancreas, Uterus and Adnexa and Pituitary Gland: These organs presented a normal histologic picture.

Brain and Spinal Cord: The meninges were edematous and congested. A small group of lymphocytes was present in the meninges on one lateral aspect of the medulla, and tiny groups of five to six cells were seen in a few places in the depth of the anterior fissure of the spinal cord.

The brain was only moderately congested. There was marked perivascular and some pericellular edema. Only a few minute perivascular extravasations were

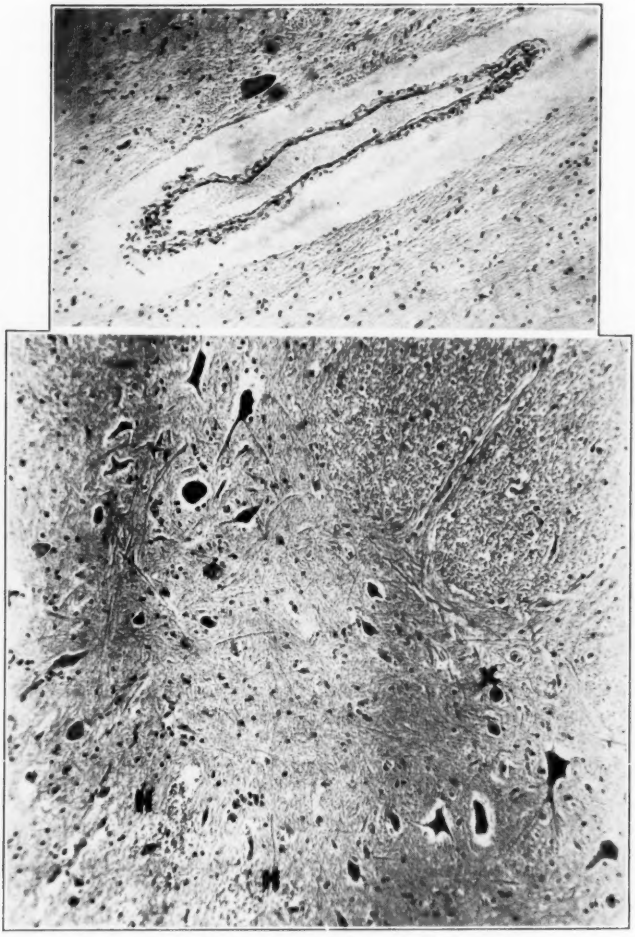

Fig. 9.—Upper illustration, vein in the basal ganglions. Only a few cells are present at each pole of the vessel, but there is no true perivascular cuffing. Cresyl violet stain; × 480. Lower illustration, lumbar cord. Several cells of the anterior horn show toxic changes. Only one small cell (x) shows severe cellular changes. There is no glial reaction. *H* indicates hemorrhage, which extends from the posterior into the anterior horn. Hematoxylin and eosin stain; × 240.

present on either side of the claustrum. Occasional ganglion cells in the frontal cortex and in the globus pallidus showed "toxic" hyperchromatic staining. In the midbrain unusual severe degenerative changes were found in most ganglion cells of the nuclei of the third and fourth nerves (fig. 7). The shape of the cells was markedly distorted, and many of them, while not enlarged, were globular and appeared to be hydropic. Their cytoplasm was extremely pale in the center and almost bluish in the hematoxylin-eosin preparations, with a narrow pink rim along the edge of the cells. In cresyl violet stain the center of the cells contained finely dispersed bluish dust and the periphery was rimmed with deeply staining remnants of Nissl substance. The nucleus in hematoxylin-eosin preparations was granular, shrunken and purplish, with a bluish nucleolus, but in cresyl violet stain it was pale and often was barely visible through the dustlike cytoplasm. There was no degeneration in the cells of the nuclei of the fifth, sixth, seventh, eighth, ninth, tenth, eleventh or twelfth nerves. In a number of Purkinje cells of the cerebellum the Nissl substances was comminuted and evenly dispersed through the cytoplasm, but the shape of the cells was not distorted. The nuclei were centrally located, and their chromatin was pushed in a semicircle toward the nuclear membrane. The nucleolus preserved its central location. In the medulla considerable degenerative changes were found in many cells of the ventral portion of the inferior reticular nucleus, on either side of the midline, just above the inferior olives. The cells were enlarged, and many were round. There was notable chromatolysis, with coarser particles of the Nissl substance on the periphery of the cells and comminution of that substance in the center, but the cells did not appear as hydropic as those in the midbrain. The eccentric nucleus was well visualized both in hematoxylin-eosin and in cresyl violet preparations. The chromatin of the nuclei appeared to be rolled up into an elongated blue mass which was pushed over to one side of the nuclear membrane, and the nucleolus was eccentrically located in the clear part of the nucleus (fig. 8). No perivascular cuffing was observed in the cortex or in the areas of cellular degeneration. Only four veins with minimal accumulations of lymphocytes over a small sector of each vessel were encountered, two in the basal ganglions (fig. 9 *A*) and two in the white matter of the cerebellum.

The gray matter of the spinal cord, from the cervical to the lumbar region, showed extensive recent perivascular hemorrhages which in many places had broken through into the nervous tissue. In the upper parts of the cord the hemorrhages were limited to the posterior horns, but in the lumbar region there also were many extravasations at the bases of the anterior horns and one or two small perivascular hemorrhages in the white matter adjoining the posterior horns, in the lateral and posterior columns. The cells of the anterior horns in the cervical and thoracic regions were intact, but in the lumbar region several cells showed "toxic" changes, and two cells in one horn were round and devoid of Nissl substance and nuclei (fig. 9 *B*); one of these cells was located in the midst of a hemorrhage. The sacral area of the cord was intact. No perivascular cuffing was found in the cord.

No neuronophagia of degenerated cells was found in the spinal cord, medulla, midbrain or cerebellum, and there was no cellular infiltration of the roots of any cranial or spinal nerves.

Myelin stains revealed no changes in the brain, medulla or spinal cord. However, there was some loss of myelin in a few fibers of an anterior root, at their emergence from the lumbar region of the cord, corresponding to the anterior horn containing a few damaged ganglion cells. The myelin of the other anterior and both posterior roots was intact.

COMMENT

The case presented here was unquestionably one of infectious mononucleosis even if the hematologic picture was not particularly characteristic. The patient's blood at no time contained more than 49 per cent lymphocytes, and even on the last day of life only 11.5 per cent of white cells were "abnormal" lymphocytes. However, the clinical picture of lymphadenopathy after a few days of illness and a rising titer of the heterophile antibody in the blood (from 1:448 to 1:1,792 and to 1:14,336) made the diagnosis of infectious mononucleosis possible despite the prevalence of neurologic manifestations earlier in the disease.

The microscopic changes in the tonsils, lymph nodes, spleen, liver, kidneys and adrenals in this case were similar to those described in biopsies (Fox,[17] Marchal and others,[7b] Gall and Stout [18]), in surgically removed spleens [19] and in the several necropsy reports available in the literature.[20] The heart and lungs were not involved. The tonsils and other faucial lymphoid tissue presented changes which were more severe than those of the lymph nodes and less severe than the changes in the spleen, in which most structures were largely obliterated by the hemorrhages and by extensive replacement of normal lymphocytes by large "abnormal" forms. Impression smears from the lymphoid organs, especially the spleen, showed the presence of "abnormal" lymphocytes in far greater numbers than in the peripheral blood.

The pathologic findings in the central nervous system in this case were of special interest because neurologic manifestations in the patient had been exceedingly severe and because the histologic changes gave a satisfactory explanation of the symptomatology. The pathologic changes consisted of selective degeneration of some nerve cells (nuclei of the third and fourth cranial nerves, Purkinje cells of the cerebellum, cells in the ventral portion of the inferior reticular nucleus) and recent hemorrhages in the gray matter of the spinal cord. The degeneration of the cells in the nuclei of the third and fourth nerves explained the diplopia which was one of the earliest clinical symptoms in the patient.

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17. Fox, H.: Infectious Mononucleosis: II. Histology of a Tonsil and a Lymph Node, Am. J. M. Sc. **173**:486 (April) 1927.

18. Gall, E. A., and Stout, H. A.: The Histological Lesions in Lymph Nodes in Infectious Mononucleosis, Am. J. Path. **16**:433 (July) 1940.

19. King.[5a] Darley and others.[5b] Davis and others.[5d] Smith and Custer.[5f] Vaughan and others.[5g]

20. (*a*) Du Bois, A. H.: De la pathogénie de l'angine à monocytes, Acta med. Scandinav. **73**:237, 1930. (*b*) Thomsen and Vimtrup.[7h] (*c*) Ziegler.[5e] (*d*) Ricker and others.[12]

The degeneration of cells in the ventral portion of the inferior reticular nucleus in the medulla is of special significance because of respiratory failure, which was the reason for the diagnosis of bulbar poliomyelitis in the terminal stage of the disease and probably also the immediate cause of death. The inferior reticular nucleus is regarded as the coordinating center of respiration, and its ventral portion has been found to be the inspiratory division of that center (Pitts, Magoun and Ranson [21]). The degeneration of the cells in that nucleus would lead to central respiratory failure. It is interesting to note that Thomsen and Vimtrup,[7h] who had clinically attributed the death in 4 of their cases to central failure of respiration, found "degeneration of cells of the center of respiration" in the medulla in 1 of those cases that came to necropsy. Respiratory failure also was the cause of death in 2 cases of Guillain-Barré syndrome in infectious mononucleosis (Ricker and others [12]), but the failure in those cases was peripheral, as it was due to the damage of the roots of the spinal nerves.

Despite the inability of the patient to move her legs, no significant changes in the neurons of the anterior horns in the spinal cord were seen. Only two cells in the anterior horn of the lumbar region of the cord showed severe degeneration, one of them located in the midst of a hemorrhage. However, spilling over of the hemorrhages from the posterior into the anterior horns in that region could explain the impairment of movements of the lower extremities.

The character of the pathologic changes in this case was degenerative rather than inflammatory, as there was no proliferative element in that process. There was no neuronophagia and not even significant satellitosis. Minute collections of lymphocytes over a part of the circumference of four veins in two distant parts of the brain would hardly be sufficient to classify this case as one of encephalitis. Nor would it be possible to call it a case of meningoencephalitis, even though there had been moderate pleiocytosis on the seventh day of illness, because no clinical meningitis was present in the last days of life and none was found in microscopic sections from the brain and cord. The clinical and pathologic findings were also different from those of polyradiculoneuritis because the protein content in the spinal fluid was low and none of the cranial or spinal nerve roots showed any lymphocytic infiltration. It would seem that the term "encephalomyelopathy" or—to include the hemorrhagic component in the spinal cord—"hemorrhagic enceph-

21. Pitts, R. F.; Magoun, H. W., and Ranson, S. W.: Localization of the Medullary Respiratory Centers in the Cat, Am. J. Physiol. **126**:637 (July) 1939.

alomyelopathy" would be most appropriate to describe the changes found in the central nervous system in this patient.

The case of Thomsen and Vimtrup,[7h] with only degenerative cellular changes, evidently also belonged in the category of encephalopathies, while the case of Allen and Kellner,[4] apparently without clinical neurologic manifestations, was one of encephalitis, because of the presence of heavy perivascular cuffing in the cerebral cortex.

As was mentioned before, the diverse neurologic manifestations in infectious mononucleosis may precede the hematologic changes and the appearance of lymphadenopathy and splenomegaly. Such cases invariably present considerable diagnostic difficulties. The manifestations may be similar to those of meningitis, encephalitis, poliomyelitis or polyradiculoneuritis. However, a great aid in the diagnosis of the underlying disease can be derived from the test for heterophile antibody, as it has been positive in practically all reported cases of infectious mononucleosis with neurologic manifestations (Tidy[6c]). It would seem advisable, therefore, to perform that test on all patients with obscure or atypical acute neurologic manifestations. A heterophile antibody titer as high as 1:14,336, as seen in our patient, is rare. According to Thomson,[22] it has been observed only three times in over 9,000 tests performed at the Research Laboratories of the New York City Health Department.

In the past twenty years 16 deaths in the course of infectious mononucleosis have been reported,[23] including the case reported here (for earlier cases see references in article by Thomsen and Vimtrup[7h]). Two of the patients were children, and 2 of the adults were females. Neurologic complications were the cause of death in 7 cases. While this number of deaths is not appalling, considering the large number of cases of infectious mononucleosis occurring annually, the deaths and the several forms of serious complications take the disease out of the category of innocuous ailments.

SUMMARY

A fatal case of infectious mononucleosis with neurologic complications is reported. The early neurologic manifestation was diplopia, which developed before the lymphadenopathy and splenomegaly. The later neurologic manifestations were those of a bulbar lesion with respiratory paralysis and lower paraplegia.

22. Thomson, A. E.: Personal communication to the authors.

23. Gooding, S. E. F.: On Glandular Fever or Infective Mononucleosis, Practitioner **127**:468 (Oct.) 1931. Jersild.[3a] Ziegler.[5c] Smith and Custer.[5f] Thomsen and Vimtrup.[7h] Ricker and others.[12] Du Bois.[20a]

In the brain there were severe degenerative changes in the nuclei of the third and fourth cranial nerves and in the inferior reticular nucleus of the medulla and some degeneration of the Purkinje cells of the cerebellum. In the spinal cord hemorrhages were present in the gray matter, mainly in the posterior horns, but in the lumbar region the hemorrhages had spread into the anterior horns as well.

The heterophile antibody reaction was positive and showed a rise in titer from 1 : 448 to 1 : 14,336.

Dr. Annis E. Thomson, of the Research Laboratories of the New York City Health Department, checked the titer of the heterophile antibody. Dr. George K. Hirst, of the Public Health Research Institute, did the virus studies on the lymphoid organs. Miss Gladys Haber prepared the histologic material.

East Fifteenth Street.

Progress in Internal Medicine

SYPHILIS

A Review of the Recent Literature

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AND
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SYPHILOTHERAPY

PENICILLIN THERAPY

(Concluded from Page 246)

For the first time in these annual reviews, penicillin has been placed first in the section on syphilotherapy. Not only do the bulk of current reports deal with the antibiotic, either alone or in combination with metal chemotherapy and/or induced fever, but during the past five years the results obtained with penicillin have been so good as to elevate it definitely to a position of superiority.

The Therapeutic Activity of Impurities in Penicillin.—Attention has been drawn in previous reviews to the fact that certain preparations of amorphous penicillin of relatively low potency and with high content of impurities possess therapeutic activity against various infections in excess of more purified amorphous, or even crystalline, preparations. Mention of this phenomenon has again been made by Rake, Dunham and Donovick [17] (see previous installment).

Hobby, Lenert and Hyman [87] found that impure penicillin was three to five times more effective than crystalline penicillin G in experimentally produced hemolytic streptococcus infections and pneumococcic infections in mice. The factor in impure penicillin which enhances the chemotherapeutic activity of penicillin G is present in the original penicillin fermentation liquor and may be demonstrated during the extraction of penicillin in those fractions in which penicillin G is recovered. Furthermore, crystalline penicillin K may enhance the activity of penicillin G. The chemotherapeutic activity of penicillins X, dihydro F and, at times, K may also be enhanced by penicillin impurities. The chemical identification of this group of so-called impurities has not been entirely accomplished.

87. Hobby, G. L.; Lenert, T. F., and Hyman, B.: Effect of Impurities on Chemotherapeutic Action of Crystalline Penicillin, J. Bact. **54**:305 (Sept.) 1947.

Welch and his associates,[88] of the Division of Penicillin Control and Immunology, Food and Drug Administration, have concerned themselves with further elucidation of this phenomenon. They have demonstrated that from 40 to 60 per cent of samples of amorphous penicillin from different manufacturers contain one or more substances, called by them "enhancement factor," which, while itself devoid of bactericidal activity in vivo, markedly enhances penicillin activity. This factor, which they identify only as "Code 19" (though it is understood that it has later been tentatively chemically identified) is heat stable and is not inactivated by penicillinase. In vivo, against Salmonella typhosa in mice, the "factor" enhances the effectiveness of each of the fractions G, X, K, F and dihydro F proportionately to their basic activity. Further studies of this phenomenon continue.

Radioactive Penicillin.—Sato, Barry and Craig [89] describe in detail their work and summarize as follows:

> The amorphous crude penicillin obtained by extraction of a culture of the mold *Penicillium notatum* grown in medium containing radioactive sulfur as a sodium sulfate has been studied by the counter-current distribution process. Crystalline benzyl-penicillin containing radioactive sulfur was readily isolated.

Howell and Thayer [90] also discussed the method of incorporation of radioactive sulfur (S^{35}) into the penicillin molecule by biosynthesis.

Mode of Action of Penicillin.—Kinetics of Penicillin Action and Therapeutic Significance of Blood Levels: Penicillin is known to be actively bactericidal in vitro, and although the body's cellular or humoral defense mechanisms probably play a contributory role in vivo, the direct bactericidal action may be largely responsible for the therapeutic activity of the antibiotic.

In an important and well documented paper, which summarizes recent work from his own laboratory and elsewhere (excellent bibliography), Eagle [91] discusses the clinical implications in syphilis and other infections of experimental pharmacologic and biologic studies. The entire article is of importance. For the purposes of this review, the following sections deserve direct quotation:

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88. Welch, H.; Randall, W. A., and Price, C. W.: The Demonstration in Amorphous Penicillin of a Non-Penicillin Factor Which Enhances Its Protective Action, J. Am. Pharm. A. (Scient. Ed.) **36**:337 (Nov.) 1947.

89. Sato, L.; Barry, G. T., and Craig, L. C.: Distribution Studies: XI. Isolation of Benzyl-Penicillin Containing Radioactive Sulfur, J. Biol. Chem. **174**:217 (May) 1948.

90. Howell, S. F., and Thayer, J. D.: Introduction of Radioactive Sulfur (S^{35}) into the Penicillin Molecule by Biosynthesis, Science **107**:299 (March 19) 1948.

91. Eagle, H.: Speculations as to the Therapeutic Significance of the Penicillin Blood Level, Ann. Int. Med. **28**:260 (Feb.) 1948.

It is clear . . . that the penicillin levels in the blood may temporarily fall below those which are bactericidal in vitro without prejudicing the outcome of treatment. It is, however, equally clear that this "penicillin-free" interval between injections cannot be unduly prolonged without permitting the regrowth of the surviving organisms to such a degree as to counteract the therapeutic effect of the preceding injection of penicillin. The maximum time for which penicillin may be permitted to fall below effective levels without affecting the outcome of treatment will vary with the recuperative power of the particular organism and its normal rate of multiplication. An instructive contrast in this respect is afforded by experimental infections with *T. pallidum* and *Diplococcus pneumoniae* type I. . . .

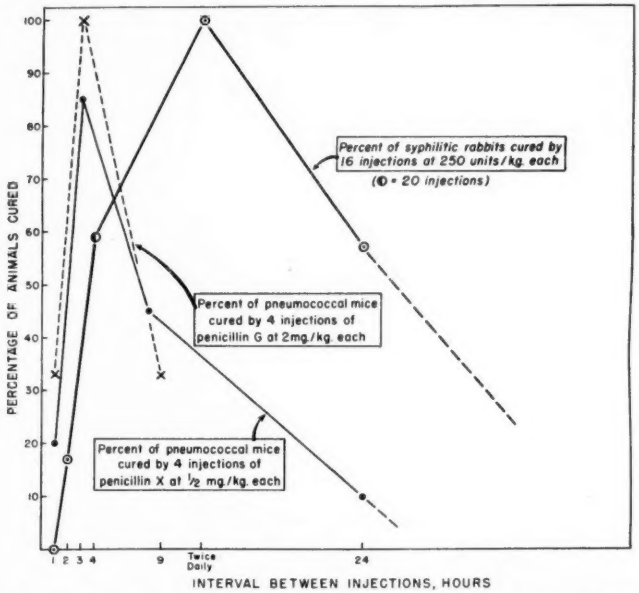

Fig. 2.—The effect of the interval between injections on the therapeutic efficacy of a given dose of penicillin. In pneumococcal infections of white mice, penicillin G or X administered at 9-hour intervals were far less effective than the same dosages administered at 3-hour intervals, due to the rapid re-multiplication of survivors in the penicillin-free interval. In the case of syphilitic infection, however, and reflecting the slow multiplication of the organisms, the interval between injections could be prolonged to 24 hours without abolishing the therapeutic efficacy of the drug. With even longer time intervals between injections, however, the organisms multiplied sufficiently in the penicillin-free interval to counteract the effect of the preceding injection. (Eagle, H.: Ann. Int. Med. **28**:270 [Feb.] 1948.)

The division time of *T. pallidum* in rabbits has been estimated, on the basis of the varying incubation periods after inocula of varying size, to be on the order of 30 hours. This is to be compared with an observed division time in vitro of 10 hours for the cultured Reiter strain of *T. pallidum*. Corresponding to this slow rate of multiplication, when syphilitic rabbits were treated intramuscularly with

16 doses of penicillin in aqueous solution, it was found that it made only a slight difference in its therapeutic activity whether the material was administered every four hours, twice daily, or even daily. The total curative doses on these three schedules were 4000 (approximately), 1770 and 4000 units/kg.; and a dose of 250 units/kg. per injection cured 50, 100 and 57 per cent of the animals, respectively. Since the latter dosage of 250 units/kg. provided a measurable level (0.03 unit) in rabbits for significantly less than two hours, it follows that when it was given only once daily, for at least 20 hours out of the 24, the blood and tissues contain insignificant and probably ineffective concentrations of penicillin. Nevertheless, the surviving organisms multiplied so slowly that even in this 20-hour "penicillin-free" period there was insufficient growth to affect the therapeutic activity of the

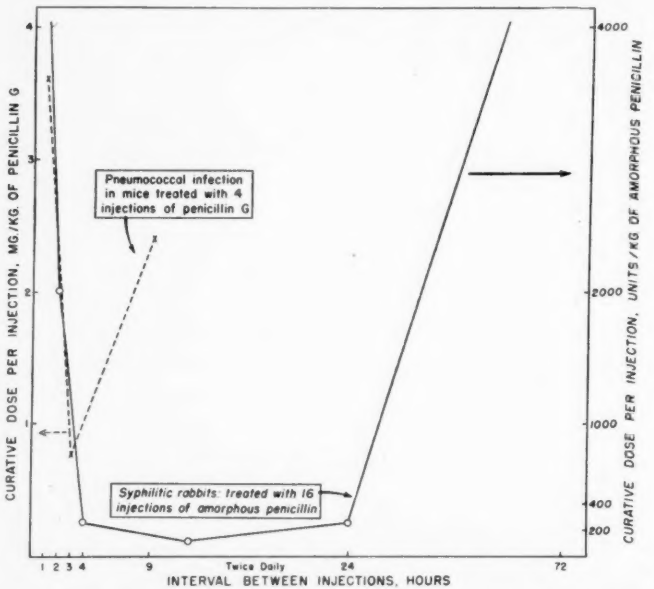

Fig. 3.—The effect of the interval between injections on the curative dose of penicillin. In pneumococcal infections of white mice, penicillins G or X administered at 9-hour intervals were far less effective than the same dosages administered at 3-hour intervals, due to the rapid re-multiplication of survivors in the penicillin-free interval. In the case of syphilitic infection, however, and reflecting the slow multiplication of the organisms, the interval between injections could be prolonged to 24 hours without abolishing the therapeutic efficacy of the drug. With even longer time intervals between injections, however, the organisms multiplied sufficiently in the penicillin-free interval to counteract the effect of the preceding injection. (Eagle, H.: Ann. Int. Med. **28**:271 [Feb.] 1948.)

preceding injection of penicillin. If, however, the interval between injections was still further prolonged, to e. g. three days, there was then ample time for multiplication, and the previously effective dose of 250 units/kg. was now wholly ineffective. Indeed, on this twice weekly schedule even dosages of 2000 units/kg. per injection failed to cure any of the animals.

A precisely similar situation was observed in the treatment of type I pneumococcal infections in white mice; but with this organism, since the average division time of the organism during the phase of active growth was 30 to 40 minutes, instead of 10 to 30 hours, the maximum time for which the penicillin blood and tissue levels could be permitted to remain below effective levels without affecting the outcome of treatment was correspondingly short. As shown in . . . figures 7 and 8, [reproduced by permission in this review as figs. 2 and 3] much larger doses were necessary to effect cure if the injections were given at nine-hour intervals than if they were repeated at three-hour intervals. Thus, when penicillin G was given every three hours for a total of four injections, a dose of 1 mg./kg. cured 80 per cent . . . of the animals; but that same dose given at nine-hour intervals cured only 30 per cent . . . With penicillin X injected at three-hour intervals a dose of 0.5 mg./kg. cured all the animals tested . . .; but given at nine-hour intervals, that dose cured only 33 per cent. . . .

In summary, although penicillin need not be maintained continuously at effective levels in order to effect cure, the maximum length of time for which those levels may be permitted to fall below concentrations which are bactericidal in vitro will vary from organism to organism. The penicillin-free interval between injections may contribute to therapy, but only so long as some of the surviving organisms continue to die, by whatever mechanism, at a rate exceeding that at which the others re-multiply. Once that therapeutically favorable balance is reversed, and once the rate of multiplication catches up with the rate at which the organisms can be destroyed, then the longer the time interval before the next injection of penicillin, the greater will be the degree to which the interim re-multiplication of organisms has counteracted the therapeutic effect of the preceding injection. . . .

In final recapitulation, Eagle says:

The blood penicillin level is of significance insofar as it provides a rough measure of the concentration at the foci of infection in the tissues. The curve of those tissue levels after an injection of penicillin is probably of major importance in relation to its therapeutic efficacy, and may be expressed in terms of three time periods; the length of time for which penicillin is present at maximally effective concentrations which kill the organisms at the fastest possible rate; the time for which penicillin is present at somewhat lower concentrations, which are more slowly bactericidal; and finally, the time period, after the penicillin has fallen to concentrations lower than those which kill the bacteria in vitro, but during which the organisms continue to die in vivo at a rate faster than they multiply. Whether this continuing death in the apparently penicillin-free interval is due to the fact that penicillin persists in the tissues longer than it does in the blood; whether organisms are killed by lower concentrations of penicillin in vivo than they are in vitro, due to the participation of the body's defense mechanisms; or whether organisms exposed to penicillin recover from its toxic effects only slowly, and during that temporary period of retarded multiplication are disposed of by the cellular and humoral defense mechanisms of the host, are as yet open questions. In any event, this third period of gradually disappearing penicillin activity provides a margin of safety, in that the blood and tissue penicillin levels may be permitted to fall below those which are significantly bactericidal in vitro without affecting the outcome of treatment.

Eventually, however, the surviving organisms do recover from the toxic effects of penicillin to the degree that they multiply faster than they can be killed, and thus counteract the effect of the preceding treatment. If this is permitted to

continue for only a brief period before the injection is repeated, the effect of treatment is counteracted only in part. More organisms are killed by each injection than reappear between injections; and provided that treatment is continued for a sufficiently long period of time, the patient may ultimately recover. If, however, too long an interval is permitted between injections, the effect of treatment may be wholly counteracted by the intervening re-multiplication of the surviving organisms. As has been indicated in the present paper, the danger is greater with organisms which recover rapidly from the toxic effects of penicillin, or which multiply at a fast rate, than it is in the case of organisms which multiply only slowly (*T. pallidum*).

Large injections of penicillin are more effective than small injections, not because they provide higher absolute levels of penicillin, but because they provide the effective concentrations for longer periods of time. More organisms are then killed by each injection, and fewer survive to re-multiply in the interval between injections. Further, that interval may then be prolonged, because with fewer surviving organisms, less harm is done by a penicillin-free interval of multplication.

It is obviously not necessary to maintain the blood and tissue concentrations of penicillin continuously at effective levels in order to attain cure. The most rapidly effective method of treatment would nevertheless be to repeat injections at such frequency as to maintain the tissue levels continuously in excess of that concentration which kills organisms at the maximum possible rate . . . However, this generalization requires qualification in at least two respects.

The first is the possibility . . . that, since bacteria are killed by penicillin only while they are multiplying, a continuously maintained level of penicillin may fail to kill those organisms which happen to be present in a physiologically inactive resting phase. Those hypothetical resting organisms ("persisters") would become vulnerable to the action of penicillin only if they were permitted to resume multiplication. . . . Intermittent treatment might therefore be more effective than continuous treatment, since the persisters would resume multiplication in the penicillin-free interval and thereby become vulnerable to the succeeding injection of the drug. There has as yet, however, been no convincing demonstration in either animals or men that intermittent treatment, i. e., periods of effective concentrations separated by penicillin-free intervals, are in fact more effective than continuously maintained levels.

The second qualification is due to the fact that certain organisms are killed more rapidly at low concentrations of penicillin than they are at high concentrations. . . . [Certain organisms] were found to give this paradoxical zone reaction. With such organisms, a continuously sustained level provided by a continuous intravenous or subcutaneous infusion might therefore be more effective therapeutically than the rapidly changing blood levels afforded by intramuscular injections of penicillin in large dosage, since with the latter method the optimally effective concentration would be present for only a short period of time.

If the thesis elaborated in the present paper is correct, then the therapeutic activity of a given dosage of penicillin rests in large part, if not primarily, on the total length of time for which it remains at bactericidal levels, with particular emphasis on the time for which it is present at the maximally effective concentration, plus the time required for the organisms to recover from the drug and effectively resume multiplication. The enormous differences observed in the curative dose of penicillin when either the number of injections or the interval between them is varied, should rest primarily on the total time period of effective penicillin action. Conversely, different schedules of treatment which have the same biological effects (e. g. 50 per cent cure in a given infection) should provide effective levels for the

same total period of time, whether the curative dose on those equi-effective schedules is 200,000 or 200 units/kg.

Blood and Tissue Levels of Penicillin in Relation to the Treatment of Syphilis.—Although, as pointed out by Tucker and Eagle,[92] it may be unnecessary to maintain a continuous bactericidal plasma concentration (especially in a disease the causative agent of which has so long a division time as T. pallidum), at present it is probably the wisest course. These workers studied penicillin levels in the serums of 138 patients after the intramuscular injection of a single dose of crystalline penicillin G in aqueous solution or in peanut oil-beeswax suspension.

The aqueous solution was given at six dosage levels (0.15, 0.3, 0.6, 1.5, 3.0 and 10.0 mg. per kilogram), totaling 18,000 to 1,200,000 units

TABLE 3.—*Frequency with Which a Given Dose of Penicillin G in Aqueous Solution Must Be Injected in Order to Maintain a Desired Plasma Level (From Tucker and Eagle[92])**

				To Maintain a Plasma Concentration of Penicillin G in Excess of						
Micrograms per cc.				0.1	0.2	0.5	1.0	2.0	5.0	10.0
Oxford units per cc.				0.16	0.32	0.8	1.6	3.2	8.0	16.0
Dosage per Kg.		Total Dose in Average Adult		The Injections Indicated in the Left Hand Column Should be Repeated at the Intervals (Hours) Indicated Below in the Body of the Table						
Mg.	Units	Mg.	Units							
10	16,700	720	1,200,000	8.0	6.0	4.5	3.5	3.0	2.0	1.2
3	5,000	216	360,000	5.0	4.0	3.0	2.0	1.6	0.6	...
1.5	2,500	108	180,000	3.0	2.5	1.7	1.2	0.8	...	...
0.6	1,000	43	72,000	2.0	1.5	0.8	...	...	...	...
0.3	500	22	36,000	1.6	0.9	...	...	...	...	...
0.15	250	11	18,000	0.9	...	...	...	...	...	...

* Tucker and Eagle say that data similar to these could not be constructed for penicillin in oil and beeswax (POB) because of greater individual variation in rate of absorption than with aqueous solution and of marked variation, as between commercial preparations, in the length of time for which they provided a plasma level. (This omission is, however, of minor importance in view of the advent of procaine penicillin.)

in the average adult. The median serum concentrations one-half, one, two, four, eight and twelve hours after the administration of penicillin at these various dosages were calculated and the degree of variation determined. The resulting curves were regular and almost linearly related to the amount of penicillin injected. At all dosages the serum concentrations fell off at the same initial rate of approximately 70 per cent per hour, but after the first few hours the concentrations fell off more slowly. With the use of these data, it was shown that it required a two and a half to tenfold increase in the dosage of penicillin in order to prolong a given penicillin plasma level by one hour.

In a table (herewith reproduced as table 3), Tucker and Eagle present data which enable the physician to determine the dosage of penicillin

92. Tucker, H. A., and Eagle, H.: Serum Concentrations of Penicillin G in Man Following Intramuscular Injection in Aqueous Solution and in Peanut Oil-Beeswax Suspension, Am. J. Med. **4**:343 (March) 1948.

(in aqueous solution) which should be administered at stated intervals in order to maintain a given concentration in the plasma. It is important to note, they point out, that the outcome of therapy with penicillin may not be prejudiced by discontinuous blood levels; optimal results may still be obtained, but in a greater total period. Since the optimum time-dose relationship for the penicillin treatment of human syphilis has as yet not been worked out, it would appear wise on the part of all, except in research and experimental centers, to attempt to maintain constant treponemicidal levels throughout the period of syphilotherapy.

As applied to syphilis, the data of this table must be interpreted, in the light of other information also supplied by Eagle,[91] as demonstrating that in experimental rabbit syphilis cure may be achieved by the frequently repeated injection of doses of penicillin too small to produce any detectable blood level at all. The treponemicidal level of penicillin, at least in the rabbit, is therefore below the smallest quantity measurable by biologic methods in blood serum (0.03 units per cubic centimeter).

Other Biologic Studies of Penicillin.—Pandalai and George [93] have shown that nucleic acid is strongly antagonistic in vitro to the bacteriostatic action of penicillin against Staphylococcus aureus. Organisms which had become nonviable after exposure to penicillin could actually be rendered viable by subsequent exposure to nucleic acid. Streptococcus viridans and Bacillus subtilis gave similar results. It is suggested that penicillin probably acts by interfering in some way with one or more phases in bacterial metabolism involving nucleic acid.

Pratt and Dufrenoy [94] point out that the penicillins inhibit susceptible bacteria more effectively both in vivo and in vitro when the environment is most favorable for growth and within wide limits their activity is not affected by the number of bacteria present. These authors agree with earlier investigators that micro-organisms which are metabolizing actively (i. e., those actively absorbing oxygen and evolving carbon dioxide) are most sensitive to the action of penicillin. At a given concentration of penicillin, organisms become more susceptible to its action as the concentration of oxygen available to the test organism is greater or as there is also present some system capable of activating the transfer of oxygen. At bacteriostatic concentrations, penicillin inhibits oxygen uptake and carbon dioxide release. The sensitive cell is induced into the lethal dehydrogenation of its essential constituents by releasing into the medium growth-promoting substances which induce nearby cells into a stage of metabolism in which they

93. Pandalai, K. M., and George, M.: A Possible Mode of Action of Penicillin, Brit. M. J. **1**:210 (Aug. 9) 1947.

94. Pratt, R., and Dufrenoy, J.: Cytochemical Interpretation of the Mechanism of Penicillin Action, Bact. Rev. **12**:79 (March) 1948.

are penicillin sensitive. It is difficult, therefore, in the opinion of these writers, to absolve the cell from a charge of collaboration, not only in its own death but in that of its relatives.

Concentration of Penicillin in Blister Fluid.—In the absence of data on the appearance or concentration of penicillin in the skin of human beings after administration of the drug, Dostrovsky, Gurevitch, and Rozansky [95] have studied the distribution, absorption and retention of penicillin in blister fluid in 20 patients. Some had cutaneous diseases characterized by formation of blisters, and in others vesicles were produced artificially by the application of cantharides. Blood and blister fluid penicillin levels were obtained at intervals of one, two and three hours respectively after administration of varied doses of the drug, given intravenously, intramuscularly or by subcutaneous injection. Blood serum and blister fluid levels were not identical, the latter, as a rule, being lower. Blister fluid maintained its penicillin level for a longer period than did the blood. Penicillin could be detected in the contents of the artificially produced blisters twenty minutes after the administration of the drug and remained measurable for up to four hours. In the contents of spontaneous blisters (pemphigus) measurable amounts of penicillin could be found as early as five minutes after injection and remained for up to six hours.

The Renal Clearance of Penicillin.—Eagle and Newman [96] summarize an article on the renal clearance of the penicillins:

1. The renal clearance of penicillins F, G, and X in man was found to approximate the total renal plasma flow and was approximately 4 to 5 times greater than the renal clearance of inulin or sodium thiosulfate. The penicillin clearance was independent of the absolute blood level over the entire range 0.05 to 10 μg. per ml. and was similarly independent of the rate of urine flow.

2. The possibility is suggested that penicillin can be used in lieu of para-aminohippuric acid or diodrast as a test of renal plasma flow and renal function.

3. The renal clearance of penicillin K in man varied from ¼ to ½ that of F, G, or X. Possible explanations for this anomalous result are discussed in the test.

4. The tubular excretory mechanism was completely saturated in 2 rabbits receiving 600 mgm. per kgm. of penicillin G. In these the initial blood levels were 2,667 and 3,200 μg.; and the initial renal clearances of 3 and 7 ml. per minute corresponded to the glomerular filtration rate. As the serum concentration fell to less than the saturation level for the tubular mechanism, the renal clearances rose to normal levels of 18 to 28 and 23 to 57 ml. per minute.

5. Although no differences were found between the renal clearance of penicillins F, G, or X, the possibility is suggested that penicillin derivatives may be produced with significantly lower clearances than those of the natural penicillins so far identified, and with correspondingly enhanced therapeutic activity *in vivo*.

95. Dostrovsky, A.; Gurevitch, J., and Rozansky, R.: A Study of the Distribution of Penicillin in Blister Fluid After Parenteral and Topical Application, J. Invest. Dermat. **10**:69 (Feb.) 1948.

96. Eagle, H., and Newman, E.: The Renal Clearance of Penicillin F, G, K and X in Rabbits and Man, J. Clin. Investigation **26**:903 (Sept.) 1947.

A possible variable source of error in assays of specimens of urine for penicillin content has been pointed out by Falk and Blech.[97] In a study of 67 specimens of urine from patients under penicillin treatment for syphilis, collected up to the fourth hour after the administration of penicillin, bactericidal activities greatly in excess of those expected from the dose injected were observed in 30 instances. In 1 case, for example, the amount of penicillin recovered in the two hour sample contained approximately twice the amount of the administered dose of penicillin in terms of bactericidal activity. Specimens collected after four hours showed expected penicillin concentrations. These high apparent levels of penicillin were not due to bactericidal activity of the urine itself or to technical errors. No explanation for the phenomenon is given.

The Administration of Penicillin by Various Routes.—Cohlan, Lewis and Seligmann[98] gave single oral doses of comparable amounts of buffered and unbuffered penicillin to 16 children and 14 infants. Penicillin blood levels were determined one and two hours after administration of the drug. Doses ranged from 3,000 to 5,000 units per kilogram of body weight. In children a buffered preparation gave a higher blood level, whereas there was no appreciable difference in the concentration of penicillin in the blood of infants, whether the preparation was buffered or unbuffered. A dose of 3,000 to 5,000 units per kilogram was effective in bringing about a "therapeutic blood level" one to two hours after administration if the buffered preparation was given to children and buffered or unbuffered preparation to infants. In vitro experiments indicated that the relatively low p_H of the gastric juice of children resulted in the destruction of penicillin, which was protected by the higher p_H of the gastric juice of infants.

Mandel[99] reports studies of rectal absorption of penicillin which demonstrate that this route is as good as absorption in the upper part of the intestinal tract but that the absorption may be enhanced by the vehicle employed. Retention enemas containing 100,000 to 1,000,000 units of penicillin resulted in insignificant levels in the blood and urine. Cocoa butter suppositories containing 500,000 to 1,000,000 units produced blood levels of 0.5 to 1 unit per cubic centimeter at fifteen minutes, with therapeutic levels persisting for several hours. Total urinary recovery averaged 6 per cent. Insufflation through an anoscope

97. Falk, C. R., and Blech, H.: Anomalous Findings in Penicillin Level Determinations in Urine, J. Lab. & Clin. Med. **32**:1356 (Nov.) 1947.

98. Cohlan, S. Q.; Lewis, J. M., and Seligmann, E.: Blood Levels of Penicillin with Oral Use of Buffered and Unbuffered Solutions: Studies on a Series of Infants and Children, Am. J. Dis. Child. **75**:15 (Jan.) 1948.

99. Mandel, E. E.: Rectal Absorption of Penicillin, J. Lab. & Clin. Med. **32**:1533 (Dec.) 1947.

of 200,000 units of penicillin produced blood levels up to 8 units per cubic centimeter at fifteen minutes. Urinary recovery ranged from 17 to 50 per cent. Cocoa butter capsules containing dry penicillin produced blood levels similar to those obtained with insufflation, with a total urinary recovery of 16 to 35 per cent. It may be remarked without facetiousness that this method of administration is likely to find no practical use in the treatment of spyhilis.

Hingson and his associates [100] conducted a study comparing hypospray and intramuscular administration of penicillin in the treatment of gonorrhea. The schedule of therapy, whether penicillin was given by injection or by hypospray, consisted of 200,000 units of crystalline penicillin G given as follows: at zero hour 50,000 units, at one hour 50,000 units and at two hours 100,000 units. The hypospray injection of penicillin was given over the biceps, triceps or deltoid muscles. Of 158 patients treated by hypospray, 97.5 per cent were cured, and of 48 treated by intramuscular injection, 97.9 per cent were cured. When hypospray instruments and cartridges are commercially available, the method is likely to prove of great value in infants and young children as distinctly less painful than intramuscular iniection with syringe and needle.

Prolongation and Enhancement of Penicillin Action.—In syphilis, more than in other penicillin-susceptible infections, it was early recognized to be of the utmost importance to develop a method of treatment which would eliminate the necessity for frequently repeated injections of aqueous solutions of penicillin; some treatment was needed which could be utilized in ambulatory patients. Previous reviews of this series have described a number of expedients calculated (*a*) to delay absorption of penicillin from the injected site or (*b*) to delay its excretion through the renal tubules. The present reviewers have pointed out, as have many others, that all efforts (until 1948) could be regarded as temporary and relatively unsatisfactory expedients, pending the development of a relatively insoluble penicillin compound, absorption of which is delayed because of its very insolubility. This goal has apparently been reached in procaine penicillin (see following paragraphs) to an extent which makes it possible to minimize the space devoted in this current review to earlier methods.

Penicillin in Absorption-Delaying Mediums.—Until the advent of procaine penicillin, the most satisfactory method of delaying the absorption of penicillin from the injected muscle mass was its administration

100. Hingson, R. A.; Easley, E. J.; Gray, A. L.; Tucker, C. B.; Kiesselbach, M. R.; Parkhurst, G. E.; Usher, G. S., and Davidson, H. H.: Hypospray Administration of Penicillin in the Treatment of Gonorrhea, J. Ven. Dis. Inform. **29**:61 (March) 1948.

suspended in a vehicle devised by Romansky and Rittman [101] consisting of peanut oil and purified beeswax, the latter in a concentration of 4.8 per cent by weight. On the basis of a series of papers by Romansky and others, it had been shown that a single intramuscular injection of 1 cc. of this mixture, containing 300,000 units, gave detectable blood levels in most persons for about twelve hours; 2 cc. (600,000 units) gave detectable levels for eighteen to twenty-two hours.

These data, furnished originally by Romansky and his associates, had rapidly been confirmed by others and in the past twelve months have found further confirmation from Cannon and his associates,[102] Trussell, Sinclair and Buchanan,[103] Hewitt,[104] Tucker and Eagle [92] and Chandler, Dowling, Romansky, Welch and their co-workers [105] The last group of investigators brought out the point that the large particle size of penicillin in oil and beeswax was desirable and important; otherwise little new information was added.

Meanwhile, it has been shown that in syphilis, both in experimental animals (Fleming and Holcombe [21] and Rosahn and Gueft [22]) and in man (Syphilis Study Section [106] and Thomas [107]), treatment schedules employing penicillin in oil and beeswax in daily injections provided results as satisfactory as those obtained with comparable dosages of the drug in aqueous solution; further evidence of this fact will be discussed presently.

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101. Romansky, M. J., and Rittman, G. E.: Penicillin Blood Levels for Twenty-Four Hours Following a Single Intramuscular Injection of Calcium Penicillin in Beeswax and Peanut Oil, New England J. Med. **233**:577 (Nov. 15) 1945.

102. Cannon, A. B.; Lindstrom, K.; Bradley, D. F.; Slatkin, M. H., and Moses, R.: Penicillin in Sesame Oil and Wax: Observations on Delayed Absorption in Sixty-Five Patients, J. Invest. Dermat. **9**:255 (Nov.) 1947.

103. Trussell, P. C.; Sinclair, S. B., and Buchanan, S. C.: Duration of Effective Blood Levels Following Administration of Penicillin in Peanut Oil and Beeswax, Canad. M. A. J. **57**:387 (Oct.) 1947.

104. Hewitt, W. L.: Serum Concentrations of Penicillin Following Administration of Crystalline Penicillin G in Peanut Oil and Beeswax, Am. Pract. **2**:247 (Dec.) 1947.

105. Dowling, H. F.; Romansky, M. J.; Welch, H.; Robinson, J. A.; Chandler, V. L.; Zeller, W. W., and Hirsh, H. L.: "Liquid" Versus "Solid" Penicillin in Oil and Wax, J. A. M. A. **135**:567 (Nov. 1) 1947. Chandler, V. L.; Romansky, M. J.; Welch, H.; Robinson, J. A.; Zeller, W. W.; Dowling, H. F., and Hirsh, H. L.: A Method for Determining the Size and Relative Weight of Penicillin Particles and Its Importance in Preparing Adequate Preparations of Liquid Penicillin in Oil and Wax, J. Am. Pharm. A. (Scient. Ed.) **37**:21 (Jan.) 1948.

106. The Status of Penicillin in the Treatment of Syphilis, Syphilis Study Section, National Institute of Health, Report to Council on Pharmacy and Chemistry, J. A. M. A. **136**:873 (March 27) 1948.

107. Thomas, E. W.: The Treatment of Early Syphilis with Penicillin at Bellevue Hospital, New York State J. Med. **47**:2439 (Nov. 15) 1947.

Interference with Urinary Output of Penicillin.—It has been shown that caronamide (4-carboxy phenylmethane sulfonanilide) delays excretion of penicillin. This compound, given orally, functions by competing successfully with penicillin at the site of tubular secretion in the kidneys.

Studies of this renal retardant have been made by Shaw, Crosson, Boger and their co-workers,[108] Strauss,[109] Seiler,[110] King and his associates[111] and Meads and his co-workers.[112] The work is, however, of academic importance only in view of the advent of procaine penicillin.

The Development of New Penicillins and Their Use in Syphilotherapy.—Early in the use of penicillin, and at a time when its chemistry was a closely guarded secret, presumably of military importance, it was recognized by chemists, pharmacologists and biologists that three major steps were desirable: (1) to purify and, if possible, to synthesize penicillin; (2) to study its possible synergism with other chemotherapeutic compounds in various infections, and (3) to develop, if possible, a chemically pure penicillin of low solubility in water (and tissue juices) in order to delay absorption and prolong penicillin action.

The purification and synthesis of benzyl penicillin (G) has been accomplished, and commercial preparations of penicillin G of at least 95 to 98 per cent purity and with a unitage of 1,500 to 1,500 per milligram are now available.

The synergism of penicillin with other chemotherapeutic compounds simultaneously administered has also been investigated in syphilis and in other infections. As to syphilis, some of the experimental data dealing with the synergism of penicillin, arsenic and bismuth are discussed in this and earlier reviews. The possible synergism of penicillin chemically combined with other agents will be mentioned presently.

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108. (*a*) Shaw, C. C.; Boger, W. P.; Crosson, J. W.; Kemp, W. W.; Ling, W. S. M., and Duncan, G. G.: Enhancement of Penicillin Blood Levels in Man by Means of a New Compound, Caronamide, Am. J. Med. **3**:206 (Aug.) 1947. (*b*) Crosson, J. W.; Boger, W. P.; Shaw, C. C., and Miller, A. K.: Caronamide for Increasing Penicillin Plasma Concentrations in Man, J. A. M. A. **134**:1528 (Aug. 30) 1947. (*c*) Boger, W. P.: Caronamide: A New Enhancing Agent for Use in Conjunction with Penicillin Therapy, Tr. Coll. Physicians Philadelphia **15**:105 (Dec.) 1947.

109. Strauss, E.: Enhancement of Plasma Penicillin Concentrations by Caronamide and Sodium Benzoate, Am. J. Med. **3**:121 (July) 1947.

110. Seiler, A. O.: Prolonging the Action of Penicillin, Bull. New England M. Center **10**:56 (April) 1948.

111. King, F. H.; Schneirson, S. S.; Sussman, M. L.; Janowitz, H. D., and Blum, L.: A Method of Producing Sustained High Penicillin Levels in the Blood, Proc. Soc. Exper. Biol. & Med. **66**:548 (Dec.) 1947.

112. Meads, M.; Long, R.; Pace, S., and Horrell, G.: Comparison in Man of Serum Levels of Caronamide and Penicillin Following Multiple Doses of the Drugs, Am. J. Med. **4**:465 (March) 1948.

A highly insoluble salt of penicillin, procaine penicillin, has been introduced within the past year; others are certain to follow. Indeed, the chemical and pharmacologic developments are proceeding so rapidly as to be far in advance of experimental or clinical therapeutic trial, especially in syphilis. It has been repeatedly pointed out that for the evaluation of a valuable new drug for treatment of syphilis at least 1,000 patients must be treated and observed over a minimum period of two years. In the five years in which penicillin has been under intensive study in the treatment of syphilis, the first three years were devoted to the only product then available, amorphous penicillin administered in aqueous solution, and the last two years to a comparison of the earlier results with those produced by crystalline penicillin G in aqueous solution or by amorphous or crystalline penicillin G in peanut oil and beeswax.

Now, and suddenly, there arrives on the scene procaine penicillin, already commercially available, which is probably soon to be followed by other preparations What shall the experimental therapeutist or the practitioner himself do under these rapidly changing conditions?

A new penicillin should not be used clinically until after thorough chemical, pharmacologic and biologic study in the laboratory. Its chemical formula and physicochemical properties should be known. If it is penicillin combined with a substance which is inherently toxic in itself (e. g., procaine, beryllium or arsenic), the acute and chronic toxicity of the new salt must be determined for various animal species. Its pharmacologic properties in terms of blood and tissue levels after administration of varying doses by various routes must be known. From the biologic standpoint, its bacterial spectrum must be worked out in vitro and in vivo.

If it is shown that the new compound is of low toxicity, that it does not enhance the possibility of sensitization either to penicillin or to its subsidiary molecule, that it produces satisfactory "therapeutic blood levels" for satisfactory periods and that its penicillin activity is essentially that of crystalline sodium or calcium penicillin G, there would seem to be no objection to utilizing it in the treatment of syphilis, on a schedule based by analogy on the results obtained from crystalline penicillin G in aqueous solution or in peanut oil and beeswax and based further on its own rate of absorption and excretion as indicated by pharmacologic studies.

This is the situation which now prevails with procaine penicillin.

Procaine Penicillin.—This salt of penicillin was developed chemically in the experimental laboratories of the pharmaceutical industry and almost simultaneously in several of them. Credit for the first preparation apparently belongs equally to Sullivan and his associ-

ates,[113] of the Lilly Research Laboratories, and Salivar and his group,[114] of Chas. Pfizer and Company, Inc.

The published papers on this preparation are as yet limited in number to those mentioned and to communications from Herrell, Nichols and Heilman,[115] Hobby, Brown and Patelski,[116] Boger and his associates [117] and (while this review was in process of final completion) Thomas and his co-workers.[118]

The situation has been proceeding so rapidly, however, that it seems wise to quote from certain papers as yet unpublished in the periodical literature. These were presented at a symposium, "Recent Advances in the Study of Venereal Diseases," held in Washington, D. C., on April 8-9, 1948, under the auspices of the Syphilis Study Section, National Institute of Health.[118a] At this symposium Welch and Hirsh [119] dealt with the pharmacology of procaine penicillin, Kitchen and others [120] with human blood levels following administration of various derivatives of penicillin suspended in various absorption-delaying vehicles

113. Sullivan, N. P.; Symmes, A. T.; Miller, H. C., and Rhodehamel, H. W., Jr.: A New Penicillin for Prolonged Blood Levels, Science **107**:169 (Feb. 13) 1948.

114. Salivar, C. J.; Hedger, F. H., and Brown, E.: J. Am. Chem. Soc., 1948, to be published.

115. Herrell, W. E.; Nichols, D. R., and Heilman, F. R.: Procaine Penicillin G (Duracillin): A New Salt of Penicillin Which Prolongs the Action of Penicillin, Proc. Staff Meet., Mayo Clin. **22**:567 (Dec. 10) 1947.

116. Hobby, G. L.; Brown, E., and Patelski, R. A.: Biological Activity of Crystalline Procaine Penicillin in Vitro and in Vivo, Proc. Soc. Exper. Biol. & Med. **67**:9 (Jan.) 1948.

117. Boger, W. P.; Oritt, J. E.; Israel, H. L., and Flippin, H. F.: Procaine Penicillin G in Oil: I. Plasma Concentrations; Preliminary Observations on Its Use in Pneumonia, Am. J. M. Sc. **215**:250 (March) 1948.

118. Thomas, E. W.; Lyons, R. H.; Romansky, M. J.; Rein, C. R., and Kitchen, D. K.: Newer Repository Penicillin Products, J. A. M. A. **137**:1517 (Aug. 21) 1948.

118a. Paper bound copies of all the papers presented at this symposium, published privately by the Venereal Disease Education Institute, Raleigh, N. C., in cooperation with the United States Public Health Service, may be obtained on request from the Executive Assistant, Syphilis Study Section, National Institute of Health, United States Public Health Service, Bethesda, Md.

119. Welch, H., and Hirsh, H. L.: The Pharmacology of Procaine Penicillin, in Symposium on Recent Advances in the Study of Venereal Diseases, Venereal Disease Education Institute and United States Public Health Service, 1948, p. 294.

120. Kitchen, D. K.; Thomas, E. W.; Lyons, R. H.; Romansky, M. J., and Rein, C. R.: Human Blood Levels Following Various Derivatives of Penicillin Suspended in Various Absorption-Delaying Vehicles, in Symposium on Recent Advances in the Study of Venereal Diseases, Venereal Disease Education Institute and United States Public Health Service, 1948, p. 288.

and Hirsh, Taggart and Welch [121] with the treatment of early syphilis with procaine penicillin suspended in oil.

The information supplied by Welch and Hirsh [119] deserves extended quotation, as follows:

Procaine penicillin in oil became available to clinicians on February 10, 1948. Prior to the preparation of a monograph under the Penicillin Regulations describing the standards of identity, strength, quality and purity of this drug, a considerable amount of study had been devoted to establishing its safety and efficacy. These preliminary studies indicated that procaine penicillin in oil would be one of the most important and valuable of the penicillin preparations for prolonging blood levels. In the two months that have followed the advent of procaine penicillin, enormous quantities have been made available for use and, in contrast to the usual gradual acceptance of a new preparation, the medical profession has rapidly adopted this form of penicillin for therapeutic use. In approximately two months, well over 3.5 trillion units of procaine penicillin in oil have been certified.

Procaine penicillin is usually prepared by the double decomposition of sodium penicillin and procaine hydrochloride. The relatively insoluble salt resulting contains approximately 40 milligrams of procaine for each 60 milligrams of penicillin. Thus, in the ordinary dose of 300,000 units, approximately 120 milligrams of procaine is injected. Procaine is the least toxic of the more widely used local anesthetics, possessing approximately one-fourth the toxicity of cocaine. If the approximate fatal dose of cocaine for man is 1.2 grams, then the lethal dose of procaine would be on the order of 4.8 grams. This would be equivalent to 12,000,000 units of procaine penicillin in a single injection. However, as much as 3.0 grams of procaine have been employed in a single surgical procedure without untoward symptoms and, in addition, the insolubility of procaine penicillin and resulting slow release of procaine would have to be considered in arriving at an approximate fatal dose of the latter drug. Furthermore, procaine is rapidly destroyed by the liver. Animals are able to withstand repeated intravenous injections of large fractions of the minimum fatal dose and several times the average fatal intravenous dose can be administered to cats by slow infusion with survival of the animals. Although no irritant or devitalizing action has been demonstrated for procaine, some individuals are extremely sensitive to the central nervous system stimulant action of procaine. In such cases, however, the onset is slow and any of the common barbiturates control the reaction. Unfortunately, deaths have been reported following the administration of as little as 0.01 to 0.13 grams of procaine, and it is therefore important to determine the allergic state of an individual toward procaine before procaine penicillin is administered. Although death in an idiosyncratic individual due to procaine has been an extremely rare occasion, consideration has to be given now to the fact that where thousands of patients are administered procaine as an anesthetic, tens of thousands will be injected with procaine penicillin.

Prior to the acceptance [by the Food and Drug Administration] of procaine penicillin in oil, at least 2,000 individuals had received injections of the drug with no evidence of sensitization. . . . There have been no authentic [later] reports of sensitization. It was expected that we would encounter not only the usual 3-6 per cent of patients sensitive to penicillin, but, in addition, those sensitive to procaine

121. Hirsh, H. L.; Taggart, S. R., and Welch, H.: Treatment of Early Syphilis with Procaine Penicillin G in Oil, in Symposium on Recent Advances in the Study of Venereal Diseases, Venereal Disease Education Institute and United States Public Health Service, 1948, p. 305.

as well. On the basis of data available to us at this time this is apparently not to be the case. Lack of sensitization to procaine penicillin may be due to the slow release of procaine as the drug breaks down in the tissues bringing about subjective relief in a manner similar to that produced by benadryl and pyribenzamine. . . .

As was previously demonstrated with other salts of penicillin, the toxicity of procaine penicillin is associated with the cation, the procaine portion of the molecule. In mice the LD_{50} of procaine base was found to be approximately 1.06 milligrams, while that of procaine penicillin was found to be 2.45 milligrams. On the basis that procaine penicillin contains approximately 40 per cent of the base, the latter figure (2.45 mg.) would appear to be within the limits of experimental error and that the toxicity observed is due to the procaine present.

Similar results were obtained in both dogs and cats with intravenous or intramuscular injection. . . .

After the injection of procaine penicillin in oil, urinary excretion of penicillin follows the same general trend that is obtained on injection of penicillin itself. . . .

The data upon which was based the claim that following the injection of 300,000 units of procaine penicillin in oil, blood concentrations of penicillin of 0.03 units or more would be obtained for 24 hours in at least 95 per cent of patients injected, were obtained from a study of 400 patients by 10 investigators.

. . . The solubility of procaine penicillin in oil appears to be insignificantly low while the solubility of procaine penicillin in water of the lots studied averaged 6500 units per ml. with very little variation from one lot to another. . . . Examination of a large number of lots of procaine penicillin in oil has indicated that all would pass the requirements which were established for penicillin in oil and wax concerning particle size, namely that not less than 50 per cent of the total relative weight of the penicillin in the drug consists of penicillin having a particle size not less than 50 microns in length. . . .

The evidence available on procaine penicillin indicates that it is one of the most important developments made by the drug industry since penicillin was first produced in this country. In addition to the fact that procaine penicillin prolongs blood concentrations of penicillin longer and at higher levels than any other previously developed product, this drug has several other advantages. On injection into the muscle, procaine penicillin appears to be less painful than the injection of aqueous solutions of sodium, potassium or calcium penicillin. This lack of pain is probably due to the slow release of procaine which results in a local anesthetic effect. In addition, the evidence available indicates that we will obtain a marked decrease in the number of individuals sensitive to this drug over those normally found sensitive to penicillin. Lack of sensitivity following injection of procaine penicillin is probably due to the procaine in the procaine penicillin molecule, but the mode of its action is not clear at the moment. . . .

Unfortunately, recent studies have indicated that the preliminary outstanding results obtained with procaine penicillin in oil have proven not to be consistent in all lots of procaine penicillin in oil produced.

The inconsistency of performance of procaine penicillin in prolongation of blood levels has still more recently been, at least in part, obviated by the addition (to commercial products of several manufacturers) of 2 per cent aluminum monostearate, a development briefly mentioned by Kitchen and his co-workers [120] and in the most recent article of Thomas and his group.[118] Data, most of which are still unpublished, indicate that in most cases a single injection of 600,000 units (2 cc.) will provide measurable blood concentrations for forty-eight

hours and a single injection of 1,200,000 to 1,800,000 units (4 to 6 cc.) for four to five days.

On the basis of this pharmacologic information, it is at least suggested that a one day single dose treatment of early syphilis may at last be in sight; clinical experiments to this end are now under way.

Hirsh, Taggart and Welch [121] report preliminary results of the treatment of 50 patients with early infectious syphilis with procaine penicillin, 600,000 units daily for five days to a total dose of 3,000,000 units. Response was similar to that obtained after treatment with aqueous penicillin or penicillin in oil and beeswax. Large series of patients treated with procaine penicillin will not be available for another two years.

Metal Salts of Penicillin.—In two brief papers, Monash [122] reports a restudy of the relatively insoluble penicillin salts produced by what is stated to be chemical combinations of penicillin and heavy metals. According to him, it is chemically possible to produce such penicillin salts, although he provides no published evidence that the preparations which he has used are actually stable chemical compounds and not mixtures. At any rate, they have not been used hitherto because of Abraham and Chain's [123] statement that such metallic ions inactivate penicillin in vitro and it was presumed that the inactivation was irreversible. To the contrary, the author has found that when an insoluble heavy metal salt of penicillin is injected intramuscularly into rabbits, the penicillin is reactivated in vivo and produces a blood level prolonged for at least twenty hours. Bismuth, silver and mercury penicillates have been shown to produce therapeutically active blood levels of penicillin for at least four times as long as soluble penicillates.

Monash reiterates, in a second communication,[122b] that it has been known that penicillin combines with a number of the metallic ions, such as copper, lead, zinc, cadmium, nickel, mercury and uranium, as well as with numerous organic substances, including triphenylmethane dyes such as gentian violet, brilliant green, crystal violet, methyl violet and basic fuchsin. It has heretofore been thought that the combination of these various substances with penicillin resulted in inactive penicillin salts. Monash has demonstrated, however, that an intramuscular injection of 20,000 units per kilogram of silver penicillate produced a blood level in the rabbit of 0.08 units per cubic centimeter at seventeen hours and 0.03 units at twenty hours. Similar injections of mercury penicillate gave a level of 0.08 units at seventeen hours and of ferric penicillate

122. (*a*) Monash, S.: The Use of Bismuth, Silver and Mercury Salts of Penicillin for the Prolongation of Penicillin Blood Levels, J. Invest. Dermat. **9**:157 (Sept.) 1947. (*b*) Monash, S.: Use of Insoluble Penicillin Salts for the Prolongation of Penicillin Blood Levels, Science **106**:370 (Oct. 17) 1947.

123. Abraham, E. P., and Chain, E.: Purification and Some Physical and Chemical Properties of Penicillin, Brit. J. Exper. Path. **23**:103, 1942.

a level of 0.16 units at seventeen hours and 0.02 units at twenty hours. The reactivation of penicillin in vivo takes place, he says, not only with inorganic but also with organic salts. An intramuscular injection in a rabbit of 20,000 units per kilogram of brilliant green penicillate produced a blood level of 1.6 units per cubic centimeter at eighteen hours and a similar injection of gentian violet penicillate a blood level of 0.04 units at eighteen hours.

From the standpoint of the syphilotherapeutist, the prospect of attaining synergistic effect by the employment of the bismuth, mercury and arsenical salts of penicillin is most intriguing.

Pratt and others [124] report that "the enhancement of penicillin effectiveness by the addition of small amounts of cobalt, previously observed *in vitro,* has been demonstrated *in vivo.*"

In a small scale clinical investigation, however, Eames and Archer [125] found no demonstrable enhancement of the penicillin plasma level when bismuth and arsenic were given concomitantly with injections of penicillin.

General Articles on Penicillin Syphilotherapy.—Several authoritative articles have appeared which embrace the entire field of penicillin in the treatment of syphilis. Although there is healthy variation in opinion, it is perhaps remarkable that there is so much uniformity. All agree that penicillin has now won for itself a permanent and important place in the armamentarium of the syphilotherapeutist; differences of opinion have mainly to do with the advisability of supplementary types of therapy in particular manifestations of syphilis.

The most important and authoritative article of the year is a semi-official report by the Syphilis Study Section, National Institute of Health, to the Council on Pharmacy and Chemistry, American Medical Association,[106] which may be summarized briefly as follows:

Available clinical and experimental evidence indicates that penicillin is relatively nontoxic for man, and no deaths clearly attributable to the drug have been reported.

The Jarisch-Herxheimer reaction is common in the treatment of all types of syphilis with penicillin. Although in either early or late syphilis the reaction is usually not serious, some deaths of infants have occurred in which the Herxheimer reaction may have been a contributing factor.

Instances of penicillin resistance in experimental and clinical late syphilis have been reported, but there is little or no evidence that

124. Pratt, R.; Dufrenoy, J., and Strait, L. A.: The Enhancement of Penicillin Effectiveness in Vivo by Traces of Cobalt, J. Bact. **55**:75 (Jan.) 1948.

125. Eames, J. W., and Archer, G. T. L.: Investigation into Possible Effect of Intramuscular Injections of Bismuth on Penicillin Content of the Blood Serum when Given Concurrently with Penicillin in Treatment of Syphilis, J. Roy. Army M. Corps **89**:57 (Aug.) 1947.

penicillin-resistant disease analogous to arsenic-resistant and bismuth-resistant syphilis exists.

Crystalline penicillin G is superior to amorphous penicillin both for experimental animals and for man. With a total dose of 4,800,000 units of crystalline penicillin G given in aqueous solution, the failure rate in early syphilis in man at the end of one year is about 10 per cent. It is suggested that if crystalline penicillin G is so used 50,000 units be given intramuscularly every two hours for ninety-six injections, a total of 4,800,000 units.

Satisfactory results may also be obtained from intramuscular injections of 600,000 units of amorphous penicillin in oil and beeswax (POB) [126] once daily for ten consecutive days, a total of 6,000,000 units. With this schedule, the failure rate is exactly comparable to that following the use of 4,800,000 to 9,600,000 units of amorphous penicillin in aqueous solution, namely, about 15 per cent.

Although experimental evidence in animals indicates an advantage if penicillin is given simultaneously with arsenic or bismuth, the benefits of such combined treatments in man are not definite. For this reason, and since the results from penicillin alone seem to be satisfactory in early syphilis, combined therapy with arsenic and bismuth preparation is not advised for the first course of treatment. If, however, treatment with penicillin alone has resulted in failure, it is suggested that 600 mg. of oxophenarsine hydrochloride and 2,000 mg. of bismuth be added to the next course of penicillin. The arsenic may be given every other day in ten intravenous injections of 60 mg. each and bismuth in intramuscular injections of 200 mg. each at intervals of every five to seven days.

It is assumed that since penicillin is an effective treponemicide in the treatment of early and many late manifestations of syphilis, it should also be effective in the treatment of late latent syphilis, though its actual efficacy as compared with, for instance, six months of metal chemotherapy will not be definitely known for a decade or more. Penicillin is no more effective than arsenic and bismuth in reducing the quantitative titer of serologic tests for syphilis.

Clinical results indicate that a total dosage of 2,000,000 to 4,800,000 or more units of penicillin is effective in healing cutaneous, mucocutaneous, osseous and hepatic lesions of benign late syphilis; late results in terms of prevention of relapse or progression are not yet available.

Until there has accumulated a large series of post-treatment observations comparing the life expectancy of patients treated with penicillin with that of patients treated with other drugs or not at all, one cannot

126. And, therefore, probably from similar dosage of procaine penicillin as well (reviewers' note).

evaluate the results of the treatment of cardiovascular syphilis with penicillin. It is suggested that since Herxheimer reactions do occur in other forms of syphilis cardiovascular syphilis be treated cautiously.[127] It may be advisable to withhold penicillin until a course of heavy metal therapy has been given. If penicillin is used, the total dosage should be large, 5,000,000 or more units. The individual dosage should be small, 25,000 to 40,000 units, and the duration of treatment prolonged to fifteen or more days.

Syphilitic iritis responds promptly to treatment with penicillin. The use of this drug in interstitial keratitis is of uncertain value. Less than half the patients so treated respond promptly. It will require years to determine the effectiveness of penicillin in the treatment of primary optic atrophy. Meanwhile, this complication should be treated with combined fever and penicillin therapy.

Penicillin is nearly 100 per cent effective in the prevention of prenatal syphilis. In any stage of the maternal infection penicillin should be used as soon as the diagnosis of concomitant syphilis and pregnancy has been established. Successful schedules in pregnant women have provided total doses of 4,000,000 to 6,000,000 units given at intervals of two to three hours over a period of eight to fifteen days.

Administration of penicillin in aqueous solution is a more satisfactory method of treating infantile congenital syphilis than other types of treatment. It is suggested that the total dose be a least 100,000 to 400,000 units per kilogram of body weight and that this total be given in divided doses every two or three hours over a period of eight to fifteen days.

The results of treating the various forms of late congenital syphilis have been essentially similar to those of treatment of patients with analogous manifestations of the acquired disease.

Penicillin exerts a markedly favorable effect on the abnormalities of the spinal fluid in all types of neurosyphilis.

A total of 4,000,000 to 10,000,000 units of penicillin alone in aqueous solution administered over a period of seven and a half to twenty-one days is suitable for the initial course of treatment for patients with early or late asymptomatic neurosyphilis, acute syphilitic meningitis, diffuse meningovascular neurosyphilis, gumma of the brain or cord and vascular neurosyphilis. A total of 10,000,000 to 20,000,000 units of penicillin administered over a period of twelve to twenty days accompanying induced malaria fever is advisable unless the latter is contraindicated, for patients with neurosyphilis entailing a serious threat to life or vital functions, e. g. dementia paralytica, tabetic form of dementia paralytica,

127. This statement of the Syphilis Study Section is probably too guarded. See Tucker and Farmer's statement later.[139]

primary optic atrophy, nerve deafness in late syphilis, nonparalytic syphilitic epilepsy and Erb's spinal spastic paraplegia.

Data are not yet available permitting a comparison of penicillin in aqueous solution with penicillin in oil and wax in the treatment of neurosyphilis.

The authors of a bulletin prepared for physicians treating veterans for syphilis have outlined a plan for the treatment of syphilis other than neurosyphilis.[128] They recognize that the suggested treatment schedules are not the final word on the subject but represent, in their opinion, the best current thought.

The following treatment schedules are suggested:

Schedule A consists of a total of 3,000,000 units of penicillin, administered in sixty individual doses of 50,000 units at three hour intervals, day and night, over a period of 7½ days.

Schedule B consists of a total of 6,000,000 units of penicillin, administered in one hundred and twenty individual doses of 50,000 units at three hour intervals, day and night, over a period of fifteen days.

Schedule C is identical with schedule B so far as dosage and method of administration of penicillin is concerned. However, in addition to the penicillin, six doses of 60 mg. of oxophenarsine hydrochloride are also given, three during the first week of treatment and three during the second week. The initial dose of this drug should not be given on the same day that penicillin is started. . . .

Schedule D consists of forty injections of oxophenarsine hydrochloride and sixteen of bismuth subsalicylate in oil given over a period of twenty-six weeks as follows: weeks 1 to 5, oxophenarsine hydrochloride twice weekly and bismuth once weekly; 6 to 10, oxophenarsine hydrochloride twice weekly; 11 to 16, a bismuth compound once weekly; 17 to 21, oxophenarsine hydrochloride twice weekly, and 22 to 26, oxophenarsine hydrochloride twice weekly and a bismuth preparation once weekly.

Dosage: Oxophenarsine hydrochloride: average dose is 60 mg., minimum 50 mg. and maximum 70 mg., the variations being made to parallel variations in body weight.

Bismuth subsalicylate in oil: average dose is 0.2 gm. of bismuth subsalicylate, the amount contained in 1½ cc. of the oily suspension.

The authors' recommended treatment schedules for their classifications of syphilis are as follows:

Stage of Syphilis	Schedule
Primary, seronegative	A
Primary, seropositive	B
Secondary	C
Secondary, relapsing (except neurologic)	C and D
Latent (early)	A
Latent (late)	B
Tertiary, mucocutaneous	B
Tertiary, osseous	B
Tertiary, ocular	B
Tertiary, visceral	B
Tertiary, cardiovascular (all types)	B
Type undetermined	B
Congenital	B

128. Leifer, W.; Padget, P.; Pillsbury, D. M., and Johnson, B., Jr.: The Management of Syphilis, J. A. M. A. **137**:1535 (Aug. 30) 1947.

All forms of treatment failure except neurologic relapse are to be treated by schedule C followed by schedule D if the latter is necessary.

In brief form Moore [129] relates most of the important facts known about antibiotics in respect to the treatment of venereal diseases, especially syphilis. He writes:

> In short, penicillin represents a major advance in syphilotherapy. There are curious and unexplained differences in its effect in various stages of syphilitic infection as it is now available. Whether the variable mixtures of commercial penicillin or crystalline penicillin G is used, it probably represents only the first faltering steps in the antibiotic therapy of this disease. There is reason to expect that further studies may replace the present product with a new and more powerful antibiotic. Pending such a development, the organized study of penicillin has provided information within four years which otherwise would have required a generation to accumulate. More important, this co-operative study has re-emphasized that gaps in the knowledge of the fundamental biology of syphilitic infection exist which must be filled in before the perfect form of treatment of syphilis can be found.

Hirsh [130] provides an excellent review of the basic principles of use of penicillin and their clinical application. Included are discussions of chemistry, pharmacology, mode of action, methods of administration (the inadvisability and lack of necessity for intrathecal use are especially stressed) and toxicity.

The Inadequacy of Large Single Doses of Penicillin in Early Syphilis.—Peters and Barton,[131] from the Chicago Rapid Treatment Center, treated 275 patients with dark field–positive primary or secondary syphilis with sodium penicillin by the continuous intravenous drip technic in amounts varying from 10,000,000 to 25,000,000 units in twenty-four hours. The majority of patients tolerated such treatment well. High levels of penicillin in the plasma were rapidly reached and easily maintained. Significant quantities of penicillin were found in the cerebrospinal fluid in the majority of patients tested. All reactions observed were transient and cleared spontaneously. Cumulative failure rates at the end of the twelve month period of observation were 67.8, 66.2, 20.5 and 35.2 for patients receiving 10, 15, 20 and 25 million units of penicillin respectively. Relapses tended to occur early; 78 per cent of the observed failures were found within a period of five months after treatment. Sixty-four per cent of the failures were diagnosed on clinical grounds and 36 per cent on serologic grounds.

129. Moore, J. E.: The Treatment of Syphilis with Penicillin, Brit. J. Ven. Dis. **24**:1 (Jan.) 1948; Antibiotics in the Treatment of Venereal Diseases, Cincinnati J. Med. **29**:263 (March) 1948.

130. Hirsh, H. L.: Penicillin: A Review of the Basic Principles and Their Clinical Application, M. Ann. District of Columbia **17**:7 (Jan.) 1948.

131. Peters, E. E., and Barton, R. L.: The Massive Intravenous Penicillin Therapy of Early Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **31**:522 (Sept.) 1947.

It is properly concluded that 10,000,000 to 25,000,000 units of penicillin given intravenously in twenty-four hours is grossly inadequate for the treatment of early syphilis.

A separate report, also from the Chicago Rapid Treatment Center, deals with 129 patients with dark field–positive primary or secondary syphilis treated by Bundesen and his co-workers [132] with 10,000,000 units of penicillin administered by intravenous drip over a twenty-four hour period. It is not clear whether these 129 cases were a part of the larger series reported by Barton and Peters,[131] though this probably was the case. At any rate, the failure rate was as reported previously (about 67 per cent in twelve months).

For comparison with these poor results, Craig and others [133] report, from the same clinic, on a group of 429 patients with dark field–positive early syphilis who were given 40,000 units of sodium penicillin intramuscularly every three hours for thirty doses over a period of 3.75 days (total dose 1,200,000 units). In only 19.8 per cent was treatment considered a failure at the end of fifteen months' observation.

Comparison of Various Schedules in Early Syphilis.—The Venereal Disease Division of the United States Public Health Service has issued a series of progress reports concerning the effectiveness of various forms of rapid treatment for early syphilis based on data furnished by fifty state and locally sponsored rapid treatment centers. The latest of these reports by Heller, Bowman and Price [134] furnishes information as to the comparative results obtainable with twenty-two different treatment schedules involving the use of penicillin alone or with the addition of metal chemotherapy or fever. The complex data provided agree in essence with previous similar reports of these and other investigators and indicate that with the most favorable methods of use of penicillin a cumulative retreatment rate at the end of twelve to fifteen months approximates 15 per cent.

Thomas [107] has summarized in tabular form the results of treating 2,577 patients with nine different penicillin schedules. He concludes that a total dosage of 1,200,000 units of commercial penicillin given over an eight day period was inadequate, even when 40 mg. of arsen-

132. Bundesen, H. N.; Loewe, L.; Craig, R. M.; Schwemlein, G. X.; Barton, R. L., and Bauer, T. J.: Therapy of Early Syphilis with Massive Doses of Penicillin, Arch. Dermat. & Syph. **56**:339 (Sept.) 1947.

133. Craig, M.; Schwemlein, G. X.; Barton, R. L.; Bauer, T. J., and Bundeson, H. N.: Penicillin in the Treatment of Early Syphilis: Four Hundred and Twenty-Nine Patients Treated with 1,200,000 Units in Ninety Hours, Ann. Int. Med. **27**:225 (Aug.) 1947.

134. Heller, J. R., Jr.; Bowman, R. W., and Price, E. V.: Rapid Treatment of Early Syphilis: Progress Report, December 1947, J. Ven. Dis. Inform. **29**:103 (April) 1948.

oxide given daily was added. Good results were obtained with 2,400,000 units of penicillin in 7.5 days. The addition of a total dose of 320 mg. of oxophenarsine hydrochloride (mapharsen®) and 0.6 Gm. of metallic bismuth did not significantly increase the rate of cure.

Of most interest in Thomas' study were the results of the treatment of 802 patients with calcium penicillin in beeswax and peanut oil. Of this number, 529 (66 per cent) had been followed for a period of nine months or longer, and 85.1 per cent of these patients obtained satisfactory results. Thomas states that these results were as satisfactory as those in a comparable group of patients previously treated with arsenoxide, fever and bismuth who were followed for a similar period.

Chope and Malcolm [135] present the administrative advantages of penicillin therapy on an outpatient basis. From the standpoint of cost it is estimated that if a patient receives twenty doses each of arsenic and bismuth the cost to the clinic for personnel and drugs is $26.83. To treat a patient in hospital for ten days with 1,800,000 units of penicillin, five doses of arsenic and three doses of bismuth costs $77.77. The cost to the clinic of treating a patient on an ambulatory basis, whether with 3,000,000 units of penicillin, five injections of oxophenarsine hydrochloride and three of bismuth or 6,000,000 units of penicillin (POB) alone administered over a period of ten days varies between $20.56 for the former schedule and $24.65 for the latter. When weekly injections of arsenic and bismuth were used, only 26.6 per cent of patients completed treatment, whereas when penicillin in peanut oil and beeswax was given on an outpatient basis, 96.6 per cent of the patients completed treatment. It was also found that the latter method permitted a much more efficient use of professional and clinic personnel.

In a paper simultaneously published in two journals, Arnold and others [136] present the results, in 728 patients with early syphilis, of treatment with 3,400,000 units of amorphous penicillin in aqueous solution (40,000 units intramuscularly every two hours for eighty-five doses). They record a cumulative "retreatment" (i. e., failure) rate of only 5.45 per cent at the end of fifteen months' observation. This is completely discrepant with the data of practically all other workers, who, using comparable schedules of administration and even larger total dosages, record failure rates (at the same time period)

135. Chope, H. D., and Malcolm, J. C.: Administrative Advantages of Rapid Syphilotherapy on an Out Patient Basis, J. Ven. Dis. Inform. **29**:173 (June) 1948.

136. Arnold, R. C.; Cutler, J. C., and Levitan, S.: Penicillin Therapy in Early Syphilis, J. Invest. Dermat. **9**:269 (Nov.) 1947. Arnold, R. C.; Cutler, J. C.; Levitan, S., and Mahoney, J. F.: Penicillin Therapy in Early Syphilis, J. Ven. Dis. Inform. **28**:241 (Nov.) 1947.

of 15 to 25 per cent for amorphous penicillin or 8 to 12 per cent for crystalline G. The conflict is certainly due, in the opinion of the reviewers, to variations in the character of the clinical material, the frequency of post-treatment observation and differences in definitions of failure. There is no reason to suppose any superiority exists for the particular total dose of 3,400,000 units or for a time interval of two hours between doses.

Lourie [137] treated a small group of patients with large individual doses of aqueous penicillin. Seventeen patients with primary and 41 with secondary syphilis were given three intramuscular injections of 500,000 units of penicillin at hourly intervals on each of five consecutive days (total dose, 7,500,000 units). Sixteen patients with primary syphilis and 24 with secondary syphilis were given two intramuscular injections of 1,000,000 units with an hour interval between injections repeated on five consecutive days (total dose 10,000,000 units). In the evaluation of the results of the study, the two groups were considered together. At the end of twenty weeks, 27 of the 33 patients with primary syphilis were seronegative (82 per cent); at the end of twelve to eighteen months, 21 (87.5 per cent) of 24 patients followed for that length of time were seronegative. Of 65 patients with secondary syphilis, 53 were followed for as long as twenty weeks, and here again 82 per cent were seronegative. Fifty were followed for from twelve to eighteen months, and of these 38 (76 per cent) had become seronegative.

Quantitative Serologic Tests in the Post-Treatment Observation of Penicillin-Treated Early Syphilis.—In the evaluation of actual and incipient treatment failure, serologic tests after treatment with penicillin are essential. Rein [138] discusses the importance of quantitative serologic examinations in the follow-up of patients with penicillin-treated syphilis as a guide in response to treatment, as a means of differentiating between serologic relapse and reinfection, as an aid in predicting impending clinical relapse and as a means of detecting masked syphilis following a penicillin-treated gonorrheal infection. Various factors which influence the length of time required to attain seronegativity include (1) stage of disease, (2) immunologic response of individual patients, (3) degree of serologic titer, (4) sensitivity of the serologic procedure, (5) type of test employed and (6) treatment schedule employed. These are discussed in detail. Rein feels that it is often possible to distinguish between relapse and reinfection by carefully conducted quantitative

137. Lourie, E. M.: The Treatment of Syphilis with Penicillin, Brit. J. Ven. Dis. **24**:11 (March) 1948.

138. Rein, C. R.: The Serologic Tests in Penicillin-Treated Syphilis, New York State J. Med. **47**:2450 (Nov. 15) 1947.

studies at frequent intervals. There is usually a progressive decline in serologic titer after penicillin therapy in patients with early syphilis. In reinfection the patient usually attained and maintained complete seronegativity, which was followed by the development of a dark field–positive lesion at a new site. A short time thereafter seropositive reactions with rapidly increasing titers developed in such patients. In relapses, however, there was noted a sudden increase in serologic titer, followed in about one month by clinical evidence of a mucocutaneous relapse in the majority of instances. In Rein's opinion, if serologic examinations of penicillin-treated patients were performed at weekly or monthly intervals, it might be possible to predict a clinical relapse about one month prior to the appearance of clinical manifestations through a progressive increase in serologic titer. He stresses the necessity for educating patients to return for serologic and clinical examinations at regular monthly intervals for at least one year after penicillin treatment.

Penicillin in Cardiovascular Syphilis.—The effects of arsenic, bismuth and the iodides in cardiovascular syphilis have not yet been completely elucidated; it is not surprising, therefore, to find differences of opinion concerning the use of penicillin alone versus penicillin plus one or more courses of preparatory metal chemotherapy. In fact, some workers feel that penicillin should not be used at all in this type of late syphilis. Several papers dealing with this problem have appeared during the past year.

Chapman and Morgan [78] report on 59 patients with syphilitic aneurysms of the aorta. For some of these (number not stated) treatment consisted of intramuscular injections of 10,000 units of penicillin followed by 15,000 units and then 50,000 units every two hours to a total of approximately 6,000,000 units. Unfortunately for any possible estimate of the effect of penicillin, the authors also gave potassium iodide orally each day and bismuth intramuscularly every other day during the course of treatment. Some patients obtained good subjective responses in the sense of relief of pain. No objective change was noted; it is implied, though not definitely stated, that there were no serious Herxheimer reactions.

Although Tucker and Farmer [139] feel that it is too soon to judge the long term results of penicillin therapy in cardiovascular syphilis, they have reported a group of patients treated with penicillin alone. They summarize as follows:

Twenty-two patients with syphilitic aortic insufficiency and 8 with thoracic aortic aneurysm were treated by the intramuscular route with sodium penicillin

139. Tucker, H. A., and Farmer, T. W.: Penicillin in Cardiovascular Syphilis: Early Reactions to Administration, Arch. Int. Med. **80**:322 (Sept.) 1947.

in aqueous solution in total dosages ranging from 2,000,000 to 15,000,000 Oxford units.

Five patients had fever (100.0 to 102.4 F.) within the first sixteen hours of treatment. Two patients with long-standing angina at rest had attacks of usual severity and frequency during and subsequent to administration of penicillin. In no instance was the treatment schedule interrupted. No significant differences in the incidence of febrile reactions or cardiovascular symptoms occurred in 9 patients receiving small initial doses (500 to 3,000 Oxford units) as compared with that in 21 patients given large initial doses (25,000 to 100,000 Oxford units) of penicillin.

Penicillin is frequently administered to patients with cardiovascular syphilis. The absence of reported severe reactions proved to be due to treatment with penicillin tends to confirm our impression that the dangers of severe untoward reactions may have been unduly emphasized. More work must be done with various dosages of penicillin in patients with cardiovascular syphilis, however, before final conclusions are justified.

Penicillin in Neurosyphilis.—Opinion is divided in regard to the proper role of penicillin in neurosyphilis. Some feel that it may be used alone; others recommend concomitant penicillin-induced fever as the treatment of choice. While it is still impossible to settle this difference of opinion on the basis of statistically significant, adequately controlled material, the currently reported series are larger, as a rule, than heretofore and follow-up studies more convincing.

A paradox of the penicillin treatment of neurosyphilis is that excellent results are obtained after the intramuscular administration of the drug in a relatively low dosage range even though penicillin cannot be demonstrated by usual technics in the cerebrospinal fluid. When massive doses are given intravenously, penicillin may surmount the hematoencephalic barrier and appear in demonstrable concentrations in the spinal fluid.

Barton and his co-workers [140] report that in a group of 83 patients with early syphilis who were treated with 25,000,000 units of penicillin by continuous intravenous drip over a twenty-four hour period penicillin could be detected in the cerebrospinal fluid of all patients five hours after completion of treatment but none was detectable twelve hours after therapy. There was an inverse proportion between the time which had elapsed after treatment and the percentage of patients with detectable penicillin in the spinal fluid.

Since results are so satisfactory in neurosyphilis after the intramuscular administration of penicillin and since its administration by the intrathecal route is distinctly dangerous, the latter method of treatment has been largely abandoned. The hazards of intrathecal treatment have

140. Barton, R. L.; Marshak, L.; Bauer, T. J., and Loewe, L.: Persistence of Penicillin in the Cerebrospinal Fluid After Massive Intravenous Administration, Am. J. M. Sc. **214**:50 (July) 1947.

again been pointed out by Walker.[141] He describes experiments carried out in monkeys in which behavior suggesting paresthetic itching developed after intrathecal administration of 20,000 units of penicillin in 1 cc. of isotonic solution of sodium chloride. In 3 of 5 of these monkeys histologic alterations were noted in the spinal cords. Similar clinical experience has been noted in man by several investigators; Walker cites 2 cases from his personal experience to illustrate types of neuroreaction to intrathecal administration of penicillin (radiculitis and myelopathy associated with chronic leptomeningeal thickening). Although such reactions usually occur when large amounts of penicillin are injected into the subarachnoid space, even moderate or small doses of the drug may sometimes cause these complications.

In spite of such experimental evidence of occasional toxic sequelae to the intrathecal administration of penicillin and the bulk of clinical evidence showing that it offers no advantage in terms of end results in the treatment of syphilis of the central nervous system over the intramuscular or intravenous routes, a few workers persist in this dangerous and unnecessary method of treatment.

Thrasher, Gosman and Bowman[142] report briefly on results obtained in 179 patients treated in this manner between 1944 and 1946. Reactions to average intrathecal doses of 20,000 units have been mainly "mild," with an occasional "moderately severe" reaction. These terms are not defined. They claim that by their method of injection a penicillin–spinal fluid mixture "can be introduced high up and into the skull." Intrathecal and intramuscular administration of penicillin plus malaria therapy was used in some cases (indications not specified) and gave the best results. This report is inadequately documented and unconvincing and is perhaps unique in the following respects: (1) paralyses associated with meningovascular neurosyphilis responded better to intrathecal administration of penicillin than to any other treatment and (2) no patient became worse (i. e., had "depression, deterioration, persistent increase in any symptoms or sign"), although their series included an unspecified number of patients with tabes dorsalis and primary optic atrophy!

After intramuscular administration of penicillin, the abnormal cerebrospinal fluids seen in cases of neurosyphilis usually respond in a characteristic pattern. Maillard and Orzel[143] applied standardized

141. Walker, A. E.: Toxic Effects of Intrathecal Administration of Penicillin, Arch. Neurol. & Psychiat. **58**:39 (July) 1947.

142. Thrasher, J. R.; Gosman, J., and Bowman, G. W.: A Second Report on Intrathecal Penicillin in Central Nervous System Syphilis, J. Indiana M. A. **41**:216 (Feb.) 1948.

143. Maillard, E. R., and Orzel, A.: The Value of Quantitative Standardized Laboratory Tests in Neurosyphilis, Am. J. Syph., Gonor. & Ven. Dis. **31**:506 (Sept.) 1947.

laboratory procedures, with which quantitatively reproducible results were obtainable, to the study of 240 patients with active neurosyphilis. The first change in the cerebrospinal fluid following penicillin therapy was a reduction in the number of leukocytes in the spinal fluid, which usually reached normal limits within six months. The decrease in the cellular elements was followed by a drop in the total protein level. Complement fixation titers and the colloidal gold reactions declined more gradually. Such findings, if continuous, were interpreted as a favorable response to therapy. The first indication of renewed activity after treatment failure was an increase in the number of lymphocytes, which was followed closely by quantitive increases in the complement fixation titers, colloidal gold values and total protein contents.

The prompt and dramatic attainment of normal values for total cell count and protein determinations after the use of penicillin in neurosyphilis is characteristic. According to the Dattner-Thomas concept, such fluids are "inactive" and indicate arrest of the pathologic process in the central nervous system. In further support of this theory, Dattner and his colleagues have published three papers during the past year. In the first of these [144] they reiterate that in their opinion the activity of the spinal fluid is a more objective criterion in the evaluation of a method of treatment in this disease than are changes noted clinically. To eliminate variables in their experiment, they chose for treatment with penicillin only patients with active spinal fluid who had syphilis for more than two years. By the term "active" they mean a fluid giving a positive reaction to the complement fixation test for syphilis and containing more than four cells per cubic millimeter of fluid. Only 6 of their patients had a total protein content of 25 mg. per hundred cubic centimeters or less. Examinations of spinal fluid were made immediately before treatment and thereafter at frequent intervals.

One hundred and fifty-one patients were treated with penicillin alone. Aliquot doses were given at three hour intervals in total amounts ranging from 2,000,000 to 9,000,000 Oxford units. One hundred and thirty-five patients, 90 per cent of whom were followed for twelve months or more, responded satisfactorily. The longest period of observation was twenty-eight months. Seventeen patients were retreated, but the writers feel that this was less a reflection on the effectiveness of penicillin than on the adequacy of the dose and that even with the small amounts of penicillin used in many cases slightly better results were achieved with penicillin than they had found after malaria treatment plus intensive arsenotherapy. They believe that penicillin alone will ultimately replace fever therapy. Their experience

144. Dattner, B.; Kaufman, S. S., and Thomas, E. W.: Penicillin in Treatment of Neurosyphilis, Arch. Neurol. & Psychiat. **58**:426 (Oct.) 1947.

has led them to adopt a schedule of 40,000 units injected intramuscularly every three hours for one hundred and fifty doses, a total of 6,000,000 units.

In the second paper of the series Dattner [145] compares results in 298 patients treated with induced malaria plus chemotherapy with those obtained by treating 193 neurosyphilitic patients with penicillin alone. With malaria plus chemotherapy, the incidence of successful results in all types of neurosyphilis varied from 74.2 to 88.5 per cent, the average being 85.9 per cent. Of the 193 patients treated with penicillin who had been followed for six months or longer, 85 per cent now had inactive spinal fluids and were considered to have achieved satisfactory results.

Finally, the same basic material is represented in slightly modified form.[146] Dattner sees no need, thus far, to fall back on methods which are far more dangerous and time consuming (such as induced fever treatment). Response to penicillin, in his opinion, "was similar to or perhaps better than that previously observed following malaria."

The Dattner-Thomas concept that activity of the spinal fluid is a more objective criterion in the evaluation of a method of treatment in neurosyphilis than is clinical improvement is challenged by many workers, including us. Improvement in the cerebrospinal fluid does not imply concomitant clinical improvement: a consideration of both clinical and laboratory results is more likely to give true and useful information. The weakness of the papers from the Dattner group lies in the lack of critically analyzed clinical data, collected in as objective a manner as possible and correlated with these laboratory findings.

In a paper of similar scope, Parkhurst and Bowman [147] analyze the therapeutic results, as measured by the findings in the spinal fluid, in 458 patients with late neurosyphilis who were treated with either mechanical hyperthermy, malaria or penicillin. One hundred and twenty-two patients were treated with hyperthermy, with from thirty to sixty hours of fever at 104 F. or above. Quartan malaria was used to treat 196 patients; 85 per cent of these had temperatures of 104 F. or above for forty or more hours. The penicillin-treated group was composed of 140 patients who were given 400,000 units of penicillin in peanut oil and beeswax daily for fifteen days, to a total of 6,000,000 units. They also received eight injections of arsenoxide and five of bismuth during this time. Slightly over 80 per cent of the patients treated

145. Dattner, B.: Treatment of Neurosyphilis, New York State J. Med. **47**:2447 (Nov. 15) 1947.

146. Dattner, B.: Neurosyphilis and the Latest Methods of Treatment, M. Clin. North America **32**:707 (May) 1948.

147. Parkhurst, G. E., and Bowman, R. W.: Treatment of Neurosyphilis at Hot Springs Medical Center, Arkansas, J. Ven. Dis. Inform. **29**:159 (June) 1948.

with penicillin and 69 per cent of those treated with malaria and hyperthermy had active spinal fluids, in the Dattner-Thomas sense, before treatment. Twenty-four months after treatment, 10 per cent of the malaria-treated patients, 15 per cent of the penicillin-treated patients and 26 per cent of the hyperthermy-treated patients still showed activity in the spinal fluid.

The great but not insurmountable difficulties to be faced in correlating clinical and laboratory data are shown in the paper of Stokes, Steiger and Gammon,[148] who report on three years' experience with use of penicillin alone for neurosyphilis. They have now treated 361 patients, observed from 90 to 1,100 days after treatment. The aggregate of all spinal fluids showed 52 to 55 per cent reduced to normal or near normal and 74 per cent markedly improved. Strikingly improved spinal fluids were obtained in 61 per cent of patients with dementia paralytica or the tabetic form of dementia paralytica, 75 per cent of those with tabes dorsalis, 73 per cent of those with meningovascular neurosyphilis and 77 per cent of those with asymptomatic neurosyphilis.

Marked symptomatic improvement (excluding unimprovable signs) was obtained in dementia paralytica in 46 per cent of the cases, in the tabetic form of dementia paralytica in 35 per cent, in tabes dorsalis in 33 per cent and in meningovascular neurosyphilis in 47 per cent. There were no striking differences between the effect of earlier lower and later higher dosage, nor was great additional effect secured by second and third courses. Nevertheless, occasional patients improved with second and third courses, and some failed despite them. There seemed to be a tendency for decided improvement in spinal fluid to level off in some 70 per cent of patients by the end of the second year. The best part of the effect was obtained in most cases within the first one hundred and twenty to two hundred days after penicillin was given. There was little tendency to relapse after administration of penicillin: 11 per cent only showed a return to the original formula of the cerebrospinal fluid.

These University of Pennsylvania workers feel that in dementia paralytica penicillin therapy "catches up" to malaria therapy by the third year, equaling it in symptomatic improvement and producing superior results on the spinal fluid. In tabetic dementia paralytica and meningovascular neurosyphilis, the results of administration of penicillin were serologically superior and clinically equal to those of malaria therapy. In tabes dorsalis, the clinical improvement was one third better than with malaria therapy in the second and third years, and normality of the spinal fluid was obtained twice as often with penicillin as with

148. Stokes, J. H.; Steiger, H. P., and Gammon, G. D.: Three Years of Penicillin Alone in Neurosyphilis, Am. J. Syph., Gonor. & Ven. Dis. **32**:28 (Jan.) 1948.

malaria in the same period of time. In asymptomatic neurosyphilis the results obtained with penicillin were the best in any category (60 to 61 per cent normal and near normal fluids).

The most important complication of penicillin therapy in neurosyphilis, Stokes and his associates agree, is the Herxheimer reaction, particularly in dementia paralytica. These workers, and unpublished data from others, indicate that in about 10 per cent of patients with dementia paralytica serious clinical Herxheimer reactions develop within the first few days of treatment with penicillin and that these reactions cannot be avoided by the initiation of treatment with small doses of the drug.

O'Leary's [149] experience with penicillin in neurosyphilis is less encouraging than that of other investigators. In his material, especially in regard to tabes dorsalis and dementia paralytica, clinical improvement has been conspicuous by its absence. He states that he has not seen a remission develop in a patient with dementia paralytica after treatment with penicillin alone. The improvement in the spinal fluid, on the other hand, may be, and usually is, striking. He emphasizes the need for further research and study.

Worster-Drought [150] concludes that penicillin has now a definite and established place in the treatment of neurosyphilis. A minimum total dosage of 3,000,000 units is suggested for all forms of neurosyphilis, with doses of 4,000,000 to 5,000,000 units or more in parenchymatous neurosyphilis. He prefers the intermittent intramuscular injection of the drug in aqueous solution at three hour intervals. In order to avoid Herxheimer reactions, it is suggested that in all forms of neurosyphilis penicillin therapy be preceded by a series of bismuth injections.

In the main, the group of writers just mentioned employed penicillin alone and used as a standard of comparison comparable series of malaria-treated patients obtained from previous experience or from the literature. The following reports deal with penicillin alone versus penicillin plus (in parallel patients treated by the same authors within the same time period) some additional type of therapy (e. g., metal chemotherapy, hyperthermy or induced malarial fever).

Curtis, Burns and Norton [151] compare the results of treatment in 75 patients with various types of neurosyphilis treated with penicillin alone with those in 43 similar patients treated with penicillin and

149. O'Leary, P. A.: Treatment of Syphilis, with Special Reference to Penicillin, Journal-Lancet **68**:96 (March) 1948.

150. Worster-Drought, C.: Penicillin in Neurosyphilis, Brit. M. J. **2**:4527 (Oct. 11) 1947.

151. Curtis, A. C.; Burns, R. E., and Norton, D. H.: Neurosyphilis: Treated with Penicillin Alone and with a Combination of Penicillin and Malaria, Am. J. Syph., Gonor. & Ven. Dis. **31**:618 (Nov.) 1947.

malaria therapy. With few exceptions, penicillin was administered in equally divided doses of 40,000 units each every three hours for one hundred injections. All patients were observed for a minimum of one year after treatment. In dementia paralytica and the tabetic form of dementia paralytica, as in the group as a whole, those who received penicillin alone tended to be patients with less advanced disease. Fifty-seven per cent of 30 such patients receiving penicillin alone and 64 per cent of 28 who received combined therapy showed clinical improvement. An identical incidence of improvement in the spinal fluids of the patients treated with penicillin alone and in those receiving combined treatment was noted (70 to 71 per cent). In tabes dorsalis, the clinical results and the improvement in the cerebrospinal fluid in 23 patients given penicillin alone were essentially the same as in 9 patients receiving both penicillin and malaria therapy. The writers conclude that, in general, patients with parenchymatous neurosyphilis respond more satisfactorily to the combined method of therapy than to penicillin alone and that combined treatment is the treatment of choice in dementia paralytica. In tabes dorsalis, however, they feel that penicillin alone may well be the treatment of choice.

Wong and Packer[152] compared the effect of penicillin alone with the effect of penicillin and malaria in the treatment of dementia paralytica. A total of 46 patients, equally divided with regard to which treatment regimen was employed, was available for study. There was no significant difference in the types of psychoses in the two groups. The average duration of symptoms of dementia paralytica in the penicillin and penicillin-malaria groups was 17.5 and 16.5 months respectively. The average number of hours of fever above 103 F. (rectal) received by the penicillin-malaria group was thirty-five. The average amounts of penicillin received by the penicillin and by the penicillin-malaria groups were 5,990,000 and 5,740,000 units respectively. The mean number of days over which the antibiotic was given was identical, 21.8 in both groups. With respect to all variables except the addition of fever therapy, the two groups were similar and thus formed an excellent basis for comparative evaluation. The results in the cerebrospinal fluid were compared for the two groups six months after treatment. At this time there was no significant difference in improvement in spinal fluid as measured by cell count, total protein, colloidal gold curve and Kolmer titer for the two groups of patients. The proportion of patients achieving 50 per cent or more clinical improvement at six to twelve months after treatment was not sig-

152. Wong, Y. T., and Packer, H.: Penicillin Versus Penicillin-Malaria in the Treatment of Dementia Paralytica, Am. J. Syph., Gonor. & Ven. Dis. **32**:212 (May) 1948.

nificantly different in the two treatment groups. Two patients of the penicillin-malaria group and 3 in the penicillin group showed relapses in the spinal fluid or in the clinical symptoms, or both, between six and twelve months after treatment. No patient in either group who had received over 3,600,000 units of penicillin relapsed during the period of observation. No significant advantage was evident from the addition of malaria therapy to the penicillin regimen since equivalent clinical and laboratory response was observed in both groups.

Rose and Solomon [153] present hitherto unpublished data from the Boston Psychopathic Hospital. The majority of their earlier patients were subjected to from four to six paroxysms of induced tertian malaria as well as given penicillin. Of the large number previously reported on who were treated with 3,000,000 units of penicillin and, at least for the majority, with malaria in addition, 36 per cent required retreatment, clearly indicating that by their standards the original treatment had been inadequate. Since the publication of those data early in 1947, 115 additional patients with symptomatic neurosyphilis were treated with 6,000,000 units of penicillin and approximately the same amount of fever (malaria) used previously. Of these, only 15 per cent have required retreatment. The increase in penicillin dosage is believed to have resulted in the improvement.

Nerve Deafness Due to Syphilis.—Loch and Tucker [154] report results obtained in the penicillin treatment of nerve deafness due to syphilis. Five patients had nerve deafness associated with acute syphilitic meningitis and 8 associated with late neurosyphilis. After the determination of base line aural acuity, amorphous penicillin was given in amounts ranging from 600,000 to 4,000,000 units. Eight neurosyphilitic patients with normal hearing and 3 with conduction deafness due to disease of the middle ear were studied under comparable conditions as a control series. Aural acuity improved promptly in patients with acute syphilitic meningitis, and the improvement was sustained. Penicillin therapy was particularly promising in patients with deafness associated with late neurosyphilis, who have been essentially unaffected by methods of treatment heretofore employed. Three such patients obtained late but significant improvement in aural acuity, and 4 others maintained their original hearing throughout the study. One patient, with congenital neurosyphilis, underwent progressive loss of hearing throughout the period of observation. The increase in hearing acuity, when it occurred, started with low tones and often showed the

153. Rose, A. S., and Solomon, H. C.: Review of Psychiatric Progress 1947: Neurosyphilis, Am. J. Psychiat. **104**:470 (Jan.) 1948.

154. Loch, W. E., and Tucker, H. A.: Penicillin Treatment of Nerve Deafness Due to Syphilis, Ann. Otol., Rhin. & Laryng. **57**:167 (March) 1948.

maximal improvement almost at once. This was usually followed later by gradual improvement in the perception of higher frequencies. In several instances perception time for bone conduction improved subsequent to administration of penicillin.

Prevention of Prenatal Syphilis.—In no other aspect of syphilis has penicillin produced results so gratifying as in the prevention of prenatal syphilis.

The status of 36 infants delivered from 36 women with early syphilis treated with penicillin is reported by Aron, Barton and Bauer.[155] Each woman was given 2,400,000 or more units of penicillin during pregnancy. Thirty-five infants were born alive, and in them congenital syphilis did not develop. In 1 instance a stillbirth occurred, which may have been due to syphilitic infection. This is a failure rate of 2.8 per cent, if the single death could be attributed to syphilis. In a strictly comparable group of 28 pregnant women with early syphilis who had been treated during pregnancy with intensive arsenotherapy in the same clinic, congenital syphilis developed in 10.7 per cent of the infants.

An excellent report on 341 babies born of 243 mothers over a fifteen year period has been written by Barnett and Read.[156] Ten syphilitic infants were found, 5 from mothers who received no syphilotherapy and 5 from mothers treated during pregnancy with varying amounts of metal chemotherapy. Twenty-one mothers had been given penicillin (12 during and 9 prior to pregnancy); all babies were healthy. They encountered no syphilis in 218 infants born of mothers given metal chemotherapy prior to pregnancy even in amounts as small as those received in one to nine injections of an arsenical (32 pregnancies). Five syphilitic babies were born of mothers treated with metals during pregnancy. Bismuth only had been given to 1 mother, one to four injections of arsenic to 1, five to nine injections to 2 and more than ten to the fifth. Delivery of the entire group of 10 syphilitic infants occurred when the maternal disease was less than four years old in 5 instances and "probably recent" in 4; the other mother had stigmas of congenital syphilis. This last patient was untreated, and the case was the only one observed in which the infection in a late stage in the mother was transmitted to the child. Comparative maternal and cord blood reactions to serologic tests are tabulated. It was found that when the maternal reaction to a serologic test was positive (163 mothers) the reaction of the cord blood was positive in 40 per cent of the offspring. In 14 per cent of babies of 150 seronegative mothers serologic tests of the

155. Aron, H. C. S.; Barton, R. L., and Bauer, T. J.: Prenatal Syphilis: Its Prevention by Use of Penicillin in Treatment of Pregnant Women with Early Infectious Syphilis, Arch. Dermat. & Syph. **56**:349 (Sept.) 1947.

156. Barnett, C. W., and Read, J. M.: Syphilis in Pregnancy, California Med. **68**:432 (June) 1948.

cord blood gave positive results. The authors conclude that the policy of treating every mother who has or ever had syphilis throughout each pregnancy is unjustified, even with a drug so nontoxic as penicillin, since the hazards of syphilis in pregnancy are by no means as great as they have usually been considered to be.

In previous reviews it has been suggested that the optimum method of treatment for syphilitic pregnant women is with penicillin in aqueous solution in a total dose of 2,400,000 to 4,800,000 units given at two to three hour intervals over a seven to eight day period. Ingraham and his associates [157] have compared the results, in regard to both mother and infant, in 92 women treated in this manner with aqueous penicillin and in 46 treated with a total dose of 4,800,00 units of penicillin in oil and beeswax given over a nine day period. In each of these groups 2 syphilitic infants resulted, a failure rate of 2.2 per cent for aqueous penicillin and 4.9 per cent for penicillin in oil and beeswax. These differences are not significant. The response of the mothers was essentially identical with the two treatment systems. The authors feel, however, that there is some indication that penicillin in oil and beeswax is less effective for infectious early syphilis in late pregnancy after the fetus is already infected. In this situation they think that better results may be more uniformly obtained from the use of aqueous penicillin in hospitalized patients.

Penicillin in Infantile Congenital Syphilis.—Moon-Adams and Marker [158] present a discussion of the treatment of early congenital syphilis with penicillin based on 69 infants, 54 of whom were less than 1 year of age. Remarkably, their material includes 6 infants whose mothers received penicillin during the pregnancy in question, though this evidence of failure of maternal treatment with penicillin (out of line with the almost invariably successful results reported by others) is not related to the total number of syphilitic mothers treated during pregnancy with penicillin. The results of treatment of the infants conform to previous favorable reports: mortality rate 7.2 per cent; incidence of satisfactory outcome in 43 adequately followed cases, 90.7 per cent. From their own and other data, they believe that a total dose of at least 100,000 units per kilogram should be employed in infantile congenital syphilis, given at three hour intervals over a fifteen day period.

Penicillin in Late Congenital Syphilis.—The most frequent serious manifestation of late congenital syphilis is interstitial keratitis. The

157. Ingraham, N. R., Jr.; Rose, E. K.; Beerman, H.; Wammock, V. S.; Stokes, J. H., and György, P.: Treatment of the Syphilitic Pregnant Woman with Penicillin in Oil-Beeswax: A Comparison with Results Obtained Using Aqueous Sodium Penicillin, J. Ven. Dis. Inform. **28**:155 (Aug.) 1947.

158. Moon-Adams, D., and Marker, C.: Penicillin Treatment of Early Congenital Syphilis, New York State J. Med. **48**:1245 (June 1) 1948.

hope that penicillin might be of great value in this condition has not been realized. The best article thus far published is by Klauder,[159] who presents the results of the penicillin treatment of 59 patients with active interstitial keratitis followed for one to three years and evaluated in terms of final visual acuity with refraction. Only 25 of these 59 patients received penicillin alone. Nine patients were given penicillin combined with eight to twelve bouts of induced fever, 21 patients received penicillin, fever and chemotherapy and 4 patients penicillin and chemotherapy without fever. Most patients were given about 2,400,000 units of penicillin parenterally. Some also had local treatment with penicillin either by conjunctival instillations or by iontophoresis.

Penicillin, with or without other measures of treatment, did not prevent involvement of the second eye. At onset of treatment 24 of the

TABLE 4.—*Final Visual Acuities of Patients Treated with Penicillin Compared with Final Visual Acuities of Patients Treated by Other Methods and Untreated Patients (From Klauder [159])*

Method of Treatment	Reported by	Number of Eyes	Percentage Final Visual Acuity		
			6/6-6/21	6/30-6/60	Less Than 6/60
Untreated	Carvill and Derby	170	55.7[a]	25.6[b]	18.4
Untreated	Klauder and Vandoren	185	51.1	37.0	12.0
Mercury only	Schott	112[d]	55.8	24.4	19.8
Arsenic and mercury	Schott	133[d]	59.8	21.9	18.3
Arsenic and mercury	Carvill and Derby	178	84.2	11.8	3.9
Arsenic and bismuth or mercury	Hoehne	110[e]	58.0[e]	35.0[f]	7.0
Fever and chemotherapy	This study, table II	95	84.2	8.4	7.4
Penicillin	This study, table I	97	84.5	11.3	4.2

[a] a, visual acuity, 6/6-6/15; b, visual acuity, 6/21-6/60; d, visual acuity of better eye; e, visual acuity, 6/6-6/12; f, visual acuity, 6/15-6/60.

59 patients had active unilateral interstitial keratitis, and in 10 of these the second eye later became involved at intervals ranging from six weeks to six months after the original treatment. Klauder compares the final visual acuity of penicillin-treated patients with or without the aforementioned supplementary procedures with the final visual acuity of patients treated by other methods and with that of untreated patients (table 4).

These data indicate that the addition of penicillin to older methods of therapy of interstitial keratitis does not give superior results. Neither penicillin nor any other form of treatment employed eliminated the devastating effect of interstitial keratitis, industrial blindness (final

159. Klauder, J. W.: Treatment of Interstitial Keratitis with Particular Reference to the Results of Penicillin Therapy, Am. J. Syph., Gonor. & Ven. Dis. **31**:575 (Nov.) 1947.

visual acuity of 6/60 or less). Klauder feels that fever therapy is the most effective form of treatment of interstitial keratitis. He believes that penicillin can displace metal chemotherapy largely because of its nontoxicity, convenience and equality (though not superiority) of therapeutic effect. Routine treatment of interstitial keratitis at Wills Hospital at present is eight to twelve febrile paroxysms given conjointly with 2,400,000 units of penicillin in about eight days.

Treatment Failures.—As is true with all therapeutic measures heretofore employed in syphilis, all patients do not achieve optimal results from penicillin. Reynolds [160] presents certain theoretic considerations which suggest that penicillin ultimately may prove to be less efficacious against T. pallidum in the later stages of syphilitic infection than during the more acute early phases. For all susceptible bacteria thus far tested, penicillin has been found to be active in vitro against rapidly multiplying organisms in the stage of active growth but inactive against the same organisms in the resting phase. If the action of penicillin on T. pallidum is comparable to that on bacteria, it is not unreasonable to anticipate that this antibiotic preparation may prove to be of limited value in later stages of syphilitic infection. In support of this concept, Reynolds presents a variety of treatment failures, including failure of late syphilitic manifestations to heal and failures due to clinical progression despite therapy, to recurrence of lesions following an initially favorable response or to the subsequent development of new and different manifestations of syphilis elsewhere in the body.

To illustrate penicillin resistance in late syphilis he cites examples: a patient with an extensive gumma involving the nasal septum and hard palate which failed to respond to 2,400,000 units of penicillin and Hahn's case of a gumma of the penis which failed to improve after administration of 4,800,000 units of penicillin but which healed promptly on institution of arsenobismuth therapy.

As examples of clinical progression, despite penicillin therapy, Reynolds cites failure of response of the spinal fluid in 6 of 82 patients with late asymptomatic neurosyphilis treated with penicillin alone, increase in psychosis in 6 of 24 patients with dementia paralytica treated with penicillin alone, progression of tabetic symptoms in 6 of 33 patients with tabes dorsalis treated with penicillin alone, failure of improvement in cases of Erb's syphilitic spastic paraplegia and Klauder's cases of primary optic atrophy in which there was no uniform benefit from penicillin therapy. He presents also 3 cases of recurrence of lesions of late syphilis following treatment with penicillin, two being benign late lesions and the third recurring attacks of interstitial keratitis and nerve deafness.

160. Reynolds, F. W.: Treatment Failures Following the Use of Penicillin in Late Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **32**:233 (May) 1948.

There is further described a patient originally treated for asymptomatic neurosyphilis with 8,000,000 units of penicillin in whom syphilitic aortic regurgitation subsequently developed.

Willcox [161] and Scully, Falk and Stokes [162] studied large groups of patients with latent and various forms of late syphilis with respect to their blood serologic response to penicillin therapy. Less than 10 per cent attained seronegativity, and repeated courses of penicillin did not produce results superior to those after one course. These data confirm the previously published statements of many other workers that penicillin is no more effective in producing blood serologic reversal in late syphilis than the older forms of treatment.

Penicillin in Other Spirochetal Diseases.—In a preliminary paper published in 1946 the immediate results of penicillin therapy in 500 patients with primary and secondary yaws were reported by Dwinelle and his associates. In a later report [163] these same workers analyze the results of treatment of 446 of the original 500 patients after clinical and serologic observations had been made for varying lengths of time up to twelve months. Three hundred and twenty (71.7 per cent) were followed for ten to twelve months after treatment. Clinical response was uniformly excellent, but serologic response was not. Only 16.6 per cent of the 446 patients were considered to show apparent cure, (e. g., complete healing of lesions together with reversal of the Kahn reaction to persistent negativity). An additional 75.1 per cent showed satisfactory progress; healing of lesions occurred together with progressive reduction of the Kahn titer to a lower level but not to seronegativity. The remaining 8.3 per cent showed unsatisfactory progress. In this last group were included cases of reinfection as well as cases of clinical and serologic relapse. The percentage of "apparent cures" was higher (26.7 per cent) in a group of hospitalized patients treated over a four day period with penicillin in aqueous solution than in two groups treated with penicillin in oil and beeswax on an ambulatory basis. Of those given a two day ambulatory treatment, 11 per cent achieved "apparent cure," and of those treated for one day, only 6.4 per cent. If in the three treatment groups "apparent cure" is combined with "satisfactory progress," the total is almost identical, 90.2, 92.9 and 92.8 per cent respectively. It is concluded that penicillin is the drug of choice in

161. Willcox, R. R.: Effect of Penicillin on Serology of Late and Latent Syphilis, Lancet **2**:8 (July 5) 1947.

162. Scully, J. P.; Falk, M. S., and Stokes, J. H.: The Serologic Response in Penicillin-Treated Symptomatic Neurosyphilis, Am. J. Syph., Gonor. & Ven. Dis. **32**:224 (May) 1948.

163. Dwinelle, J. H.; Sheldon, A. J.; Rein, C. R., and Sternberg, T. H.: Evaluation of Penicillin in the Treatment of Yaws: Final Report, Am. J. Trop. Med. **27**:633 (Sept.) 1947.

the treatment of yaws and that penicillin in oil and beeswax is of considerable public health value in countries such as Haiti, where large numbers of patients must be treated on an ambulatory basis in rural clinics.

The native population on the islands surrounding Truk atoll numbers about 5,000, who are under the medical care of the United States Navy Military Government. The total estimated number of natives infected with yaws is not stated. However, it is said that in January 1947 there were 57 new cases per thousand per month. In an effort to stop the spread of yaws among the natives, Arje [164] says that from October 1946 to June 1947 infected persons were given single intramuscular injections of 200,000 units of sodium penicillin in aqueous solution. Later the dose was increased to 300,000 units of calcium penicillin in beeswax and peanut oil. This treatment was not considered curative but merely as a stopgap measure to check the spread of yaws until the islands could be staffed with trained personnel capable of instituting curative treatment. However, even with the small amount of penicillin administered, the total number of cases of clinically active yaws was materially reduced. In June 1947 there were only 16 new cases per thousand per month.

Relapsing Fever.—Cumberland and Turner [165] describe a method for determining the relative effectiveness of penicillin species in experimental relapsing fever infections. Crystalline penicillin G was found to be significantly more active against experimental relapsing fever than crystalline penicillins F, K or X. While the results obtained by this method correlate in a general way with those obtained in experimental syphilitic infections, the test is not regarded as a reliable means of assaying the comparative activity of penicillin species against T. pallidum.

Reactions to Penicillin.—Penicillin is a remarkably nontoxic drug. Thomas, Landy and Cooper [166] state that in the treatment of over 10,000 patients with syphilis with penicllin no lethal reactions have been observed. They classify penicillin reactions in the order of their frequency into five groups, as follows:

1. Urticarias which occurred from the sixth to twelfth day after starting treatment.

2. Exacerbations of secondary syphilitic lesions, which occurred from the sixth to tenth day after starting treatment.

164. Arje, S. L.: Yaws Treated with Single Massive Doses of Penicillin, U. S. Nav. M. Bull. **47**:965 (Nov.-Dec.) 1947.

165. Cumberland, M. C., and Turner, T. B.: Comparative Effectiveness of Penicillin G, F, K and X in Experimental Relapsing Fever, Am. J. Syph., Gonor. & Ven. Dis. **31**:485 (Sept.) 1947.

166. Thomas, E. W.; Landy, S., and Cooper, C.: Reactions to Penicillin Therapy for Syphilis, J. Invest. Dermat. **10**:77 (Feb.) 1948.

3. Erythematous or papular eruptions which occurred within the first forty-eight hours after starting treatment.

4. Localized dermatitis at site of injections of penicillin which occurred after the third or fourth day of treatment.

5. Bullous dermatitis which occurred in two patients from the seventh to tenth day after starting treatment.

Urticarial reactions had an incubation period of from six to twelve days. This conforms with the usual incubation period of serum sickness. The reaction generally lasted from four to six days, and in most instances penicillin therapy could be continued in spite of the presence of urticaria. Antihistamine drugs may or may not relieve the symptoms of this reaction. In some patients recurrent attacks of urticaria developed over a period of two months after treatment had been stopped.

The second type of reaction, late exacerbation of secondary syphilitic lesions, is unique in their experience. This reaction occurs from the sixth to the tenth day after the beginning of therapy. The lesions have the appearance of an actual relapse of secondary syphilis; however, dark field examination of serum from the lesions has always given negative results. When this episode occurred, no additional treatment was given, yet the lesions disappeared or receded in four or five days.

Contact dermatitis from the preparation or administration of penicillin has previously been reported. Marsh and New [167] have found 8 cases among physicians, nurses and corpsmen. In 2 of these an erythematovesicular eruption of the face developed. The duration and amount of exposure had no relation to the onset and severity of the dermatitis. Only 1 of the patients had previously received injections of penicillin, and this without reaction. All 8 patients had positive reactions to the skin test.

Examples of severe exfoliative dermatitis following administration of penicillin are reported by Derzavis and Beinstein [168] and Shaffer.[169]

Bondy, Sheldon and Weems [170] report severe pulmonary embolism following the accidental intravenous administration of penicillin in oil and beeswax. Animal experiments indicated that the severity of the

167. Marsh, W. C., and New, W. N.: Dermatitis Due to the Preparation and Administration of Penicillin Solution, U. S. Nav. M. Bull. **48**:391 (May-June) 1948.

168. Derzavis, J. L., and Beinstein, J.: Hemorrhagic Gangrenous Exfoliative Dermatitis Following Penicillin in Oil and Beeswax: Combined Immediate and Delayed Reactions; Report of a Case, M. Ann. District of Columbia **17**:32 (Jan.) 1948.

169. Shaffer, J. O.: Generalized Exfoliative Dermatitis Due to Penicillin, New England J. Med. **238**:660 (May 6) 1948.

170. Bondy, P. K.; Sheldon, W. H., and Weems, H. S.: Pulmonary Embolism Caused by Penicillin-Oil-Beeswax: An Experimental Investigation with Report of a Near-Fatal Case, Am. J. Med. **3**:34 (July) 1947.

reaction was due to two factors—the viscosity of the oil-beeswax mixture which caused it to block large branches of the pulmonary artery and the pronounced inflammatory reaction elicited by the beeswax.

RESULTS OF CHEMOTHERAPY IN EARLY AND LATE SYPHILIS

Studies dealing with metal chemotherapy in syphilis now appear of importance only so far as they afford a base line of comparison for penicillin therapy. Dexter [171] selected for analysis 110 patients with previously untreated primary or secondary syphilis, who were given approximately thirty injections of oxophenarsine hydrochloride triweekly and concomitant bismuth weekly within a total time period of nine to fifteen weeks. The median length of observation after treatment was fourteen months. Sixty-nine and one-tenth per cent of the patients became and/or remained seronegative, while 26.4 per cent of the patients had falling titers at final observation, i.e., a total of 95.5 per cent apparently responded well to treatment. The spinal fluids of 73 patients examined at a median time of six months after the start of treatment were all normal. Serious toxic reactions occurred in 9 patients (in 4 dermatitis, in 3 late agranulocytosis and in 2 jaundice). All patients recovered. This semi-intensive method of arsenic-bismuth therapy, if completed, provided exceedingly satisfactory results in early syphilis (which are probably better than those so far obtainable from penicillin alone). The major obstacle to its use was that in this and similar studies by other workers 25 to 60 per cent of patients failed to complete treatment in spite of intensive case-holding efforts.

Kalz and Dean [172] present an analysis of 401 patients with early syphilis treated between 1937 and 1946 with some form of arsenical and 48 patients treated with penicillin. In those who were given arsenotherapy, reactions to administration of the drug, usually minor in nature, occurred in about 30 per cent of patients treated with oxophenarsine hydrochloride. Reactions to neoarsphenamine were more severe. The massive arsenotherapy method (completed in five days) is now obsolete primarily because of danger of encephalopathy. The average time required for complete seronegativity to be attained in these patients was twenty-two weeks with arsenoxide twice weekly, twenty-three weeks with massive arsenotherapy and twenty-nine to forty-three weeks

171. Dexter, D. D.: The Intensive Treatment of Early Syphilis in Nine to Fifteen Weeks with Triweekly Injections of Mapharsen (Oxophenarsine Hydrochloride) and Concomitant Weekly Injections of Bismuth: An Analysis of the Results in One Hundred and Ten Cases, Am. J. Syph., Gonor. & Ven. Dis. **31**:533 (Sept.) 1947.

172. Kalz, F., and Dean, B.: An Evaluation of Various Forms of Therapy in Early Syphilis, Canad. M. A. J. **57**:221 (Sept.) 1947.

with other arsenicals. No treatment failures were noted in patients who received arsenic twice a week. There were 25 per cent failures, however, with massive arsenotherapy and 15 to 35 per cent with other miscellaneous schemes of treatment.

In England during the war the incidence of jaundice among patients treated for syphilis was extremely high, in some centers 50 per cent or more. It was later learned that this was homologous serum jaundice transmitted by improper sterilization of syringes. Willcox [173] analyzes 556 male patients treated for primary or secondary syphilis. All patients were treated on a schedule consisting of four courses of arsenic and bismuth, a total dose of 5.85 Gm. of neoarsphenamine and 2.0 Gm. of bismuth per course. Of the 556 patients, jaundice developed in exactly one half (278). The outcome of treatment was not significantly altered by the development of homologous serum jaundice during syphilotherapy.

Jordan and Dolce [174] believe that optimum treatment of latent and benign late syphilis consists in twenty to twenty-nine injections of an arsenical compound and about forty of a bismuth compound. They are not yet convinced that penicillin alone is satisfactory in late syphilis.

Reactions to Metal Chemotherapy.—Trivalent Arsenicals: Burton [175] continues the annual reports from the United States Navy on toxic reactions following the administration of arsenicals.

Pentavalent Arsenicals: Rose and Solomon [153] take sharp issue with an answer to a query in *The Journal of the American Medical Association* [176] and to an article by Koteen,[177] in each of which the advisability of using tryparsamide in neurosyphilis is seriously questioned. In the experience of many, they say, the drug is "therapeutically effective" in a reasonable percentage of cases, in spite of the fact that pentavalent arsenicals do not destroy spirochetes until reduced in the body to trivalent form. They do not mention the subject of ocular damage, however, and with so effective and nontoxic a drug as penicillin available, the argument has a hollow ring. Tryparsamide has, as the consultant stated in his response to the query, now been abandoned by many large research syphilis clinics throughout the country, including our own.

173. Willcox, R. R.: The Effects of Syringe-Transmitted Jaundice on the Outcome of the Treatment of Early Syphilis, Brit. J. Ven. Dis. **23**:121 (Sept.) 1947.

174. Jordan, J. W., and Dolce, F. A.: Treatment of Late Acquired Syphilis Other Than Neurosyphilis, New York State J. Med. **47**:2443 (Nov. 15) 1947.

175. Burton, O. L.: Toxic Reactions in the Treatment of Syphilis in the United States Navy in 1946, U. S. Nav. M. Bull. **47**:1095 (Nov.-Dec.) 1947.

176. Treatment of Neurosyphilis, Queries and Minor Notes, J. A. M. A. **135**:198 (Sept. 20) 1947.

177. Koteen, H.: The Present Status of Tryparsamide in Syphilotherapy, Am. J. M. Sc. **213**:611 (May) 1946.

Use of BAL in Metal Poisoning.—Gold [178] discusses briefly the rationale and pharmacology of dimercaprol (BAL; 2, 3 dimercaptopropanol) particularly with reference to arsenical derivatives.

From Eagle's laboratory come data concerning the toxicity of several antimony compounds and evidence that dimercaprol has a protective action against experimental antimony poisoning.[179] After single intravenous injections into rabbits, the lethal (LD_{95}) doses of fuadin,* tartar emetic, antiomaline* and p-methylphenylstibonic acid were found to be 150, 15, 12 and 10 mg. per kilogram respectively. By the use of dimercaprol, approximately half of the animals given otherwise lethal doses of these antimonials were saved. As is the case with arsenicals, the protective action of dimercaprol in experimental antimony poisoning was associated with and probably due to a significantly increased urinary excretion of antimony. This favorable effect on antimony excretion persisted for from two to four hours, and the authors suggest the desirability of repeating injections of dimercaprol at intervals of approximately four hours if it is used therapeutically in cases of antimony poisoning.

DeOreo [180] has demonstrated the anticipated fact that the simultaneous administration of arsenic and 2,3 dimercaptopropanol (BAL) not only detoxifies the arsenic but also destroys its therapeutic efficiency. He treated 5 patients with dark field–positive early syphilis with combined oxophenarsine hydrochloride and BAL. BAL was given in a dosage of 200 mg. six hours before arsenical therapy was started and at six hour intervals thereafter. Oxophenarsine hydrochloride was employed in a dosage of 2.2 mg. per kilogram of body weight. Injections of this drug were given daily. In 2 cases T. pallida were present on dark field examination for 3.5 days after the institution of treatment, and in 1 case for as long as eight days. Treponemes quickly disappeared from the lesion of 1 patient after one injection of BAL was withheld.

Ercoli and Wilson [181] have also demonstrated the same loss of therapeutic action when oxophenarsine hydrochloride and BAL were given concurrently in mice infected with Trypanosoma equiperdum.

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178. Gold, H.: BAL (British Anti-Lewisite), editorial, Am. J. Med. **4**:1 (Jan.) 1948.

179. Eagle, H.; Germuth, F. G., Jr.; Magnuson, H. J., and Fleischman, R.: The Protective Action of BAL in Experimental Antimony Poisoning, J. Pharmacol. & Exper. Therap. **89**:106 (Feb.) 1947.

180. DeOreo, G.: Suppression of Treponemicidal Action of Arsenic with 2,3-Dimercaptopropanol (BAL): Report of Clinical Observations in Five Cases, Arch. Dermat. & Syph. **56**:695 (Nov.) 1947.

181. Ercoli, N., and Wilson, W.: Influence of BAL on the Toxicity and Chemotherapeutic Activity of Mapharsen, J. Pharmacol. & Exper. Therap. **92**:121 (Feb.) 1948.

Holley [182] has used BAL in 12 patients in whom agranulocytosis developed after arsenotherapy for syphilis, with what he believes to be favorable results. Danby,[183] Kasdon and Shapiro,[184] Kennedy and Hennington [185] and Charleton, Peters and Thompson [186] discuss the use of BAL in various types of arsenical intoxication (chiefly encephalopathies and dermatitides).

INDUCED FEVER THERAPY

Most workers in the field of syphilis and its treatment feel that, at least for the time being, the syphilologist should be to some degree a malariologist. In the field of basic malariology there have been two signal advances in the past year. The first of these is of direct interest to the physician concerned with the induction of malarial fever in patients with neurosyphilis who has heretofore been forced either to keep active a large neurosyphilis service or to send away periodically for blood for inoculation.

As a result of the successful freezing and thawing of blood containing parasites of tertian malaria, with the production of induced Plasmodium vivax malaria in patients to whom the thawed blood was administered intravenously, Saunders and Scott [187] suggest that the method may be used to provide a blood bank of malaria parasites for use in malaria therapy for neurosyphilis and for preserving strains of human plasmodia for experimental purposes. Small, temperature-resistant containers holding 5 cc. of malaria blood were immersed in an alcohol–dry ice mixture (—75 C.) and rotated by hand until the blood solidified. The tubes were then stored at —50 to —70 C. in a dry-ice box. For thawing, prior to inoculation, the tubes were placed in a water bath at a temperature of 40 to 42 C. until liquefaction was complete.

182. Holley, H. L.: The Use of BAL (2,3-Dimercaptopropanol) in the Treatment of Agranulocytosis Following Intensive Arsenotherapy for Syphilis, Ann. Int. Med. **27**:231 (Aug.) 1947.

183. Danby, C. W. E.: Use of BAL in Arsenical Encephalopathy, Canad. M. A. J. **58**:284 (March) 1948.

184. Kasdon, S. C., and Shapiro, M. W.: Post Arsenical Encephalopathy in the Treatment of Syphilis in Women, New England J. Med. **238**:282 (Feb. 26) 1948.

185. Kennedy, C. B., and Hennington, V. D.: Drug Reactions and Their Treatment of Arsenical Dermatitis with Dimercaptopropanol (BAL), Quart. J. Med. Orleans M. & S. J. **100**:209 (Nov.) 1947.

186. Charleton, A. B.; Peters, R. A., and Thompson, R. N. S.: The Treatment of Arsenical Dermatitis with Dimercaptopropanol (BAL), Quart. J. Med. **17**:49 (Jan.) 1948.

187. Saunders, G. M., and Scott, V.: Preservation of Plasmodium Vivax by Freezing, Science **106**:300 (Sept. 26) 1947.

The second interesting advance is perhaps of less practical importance. From the London School of Hygiene and Tropical Medicine, Shortt and his co-workers present three papers [188] describing for the first time the preerythrocytic stage of mammalian malaria. This was accomplished by permitting over 500 heavily infected Anopheles maculipennis atroparvus mosquitoes to feed on a rhesus monkey. Thereafter the entire batch of mosquitoes was ground up and injected, half into the thigh muscles and half intraperitoneally, into the same monkey. The monkey was killed seven days later, and schizonts of Plasmodium cynomolgi were demonstrated in sections of the liver. Because this parasite resembled so closely P. vivax, it was reasonable to infer that a similar train of events occurred in the human infection. Accordingly infection was produced by permitting a large number of the same species of mosquitoes infected with P. vivax to feed on a patient requiring induced malaria therapy. A large number of salivary glands from infected mosquitoes were injected intravenously. Seven days after the first mosquito feeding, biopsy was performed on the liver, and the material, when examined in sections, revealed the presence of schizonts. Excellent illustrations of these forms in color are provided.

Kaplan and Read [189] point out that the technical aspects of induced malaria in the treatment of neurosyphilis have been inadequately appreciated, even in many institutions currently concerned with its use. Reliance on the arbitrary time-worn use of routine inoculums of 5 to 10 cc. of infected blood, with lack of attention to immune mechanisms involved, in the use of different malaria strains among other things has resulted in irregular, unpredictable infections often difficult to evaluate with respect to therapeutic adequacy. Since, in the opinion of these workers, penicillin has by no means outmoded the usefulness of inoculation malaria in neurosyphilis, particularly the more grave varieties, advantage should be taken of certain technical advances which have been recently made. These writers base their experience on a total of more than 450 patients with neurosyphilis who were treated with induced malaria at the Finney General Hospital Neurosyphilis Center in Thomasville, Ga. Every clinical variety of neurosyphilis was encountered, but the majority of patients were asymptomatic.

188. Shortt, H. E.; Garnham, P. C. C., and Malamos, B.: Pre-Erythrocytic Stage of Mammalian Malaria, Brit. M. J. **1**:192 (Jan. 31) 1948. Shortt, H. E.; Garnham, P. C. C.; Covell, G., and Shute, P. G.: Pre-Erythrocytic Stage of Human Malaria, ibid. **1**:547 (March 20) 1948. Shortt, H. E., and Garnham, P. C. C.: The Pre-Erythrocytic Development of Plasmodium Cynomolgi and Plasmodium Vivax, Tr. Roy. Soc. Trop. Med. & Hyg. **41**:785 (May) 1948.

189. Kaplan, L. I., and Read, H. S.: Technical Aspects of Therapeutic Malaria, Am. J. Med. **4**:846 (June) 1948.

Nine strains of plasmodia were utilized for inoculations—five strains of P. vivax, three of Plasmodium malariae and one of Plasmodium falciparum. Technics of inoculation included application of infected mosquitoes and the intravenous or intradermal inoculation of infected blood.

The writers give in detail the method of performing quantitative parasite counts and point out that such procedures eliminate confusion and wasted time in the use of therapeutic malaria by materially aiding in the determination of the severity of the given malaria infection and the degree of the patient's resistance, rapidly forecasting an immune response requiring intervention and retreatment without wasteful weeks or months of observation and in the more precise regulation of the febrile course. They point out that heterologous strains of P. vivax have been shown to produce sufficient clinical activity in persons previously infected with P. vivax to allow their routine use for the reinoculation of white patients with neurosyphilis experiencing partial immune types of original infection (five to eight paroxysms), thus eliminating the undesirable use of quartan strains for reinfection. Set criteria for malaria inoculations in the treatment of neurosyphilis have been established: (1) white patients with a history of malaria, persons from the Mediterranean area, Puerto Rico or highly endemic malaria zones and all Negroes should be primarily infected with quartan malaria intravenously in large doses (more than ten million parasites); (2) all other white patients with a history of malaria should be primarily infected with vivax malaria intravenously in doses of one million parasites; (3) patients in group 2 in whom partially immune responses, with less than five paroxysms, develop should be reinfected with quartan malaria; (4) patients in whom partially immune responses, with five to eight paroxysms, develop should be reinfected with heterologous strains of P. vivax.

Finally, these writers discuss the use of sodium bismuth thioglycollate (thiobismol®), which inhibits partially grown parasites, and point out that it can be employed to regulate both vivax and quartan infections when irregular cycles occur.

A similar discussion has also been presented by Bylmer and Winckel,[190] who describe induced malarial fever as employed by them in Amsterdam.

Whether application of infected mosquitoes is a wise procedure, in view of World War II experience with relapsing benign tertian malaria, would appear to be doubtful. The alternative method, intravenous inoculation of blood from an infected donor, is the better one. As

190. Bylmer, J., and Winckel, C. W. F.: Induced Malaria for Treatment of General Paralysis, J. Trop. Med. & Hyg. **51**:27 (Feb.) 1948.

stated in editorial form,[191] in the case of P. vivax benign tertian malaria parasites probably persist one to three years in the tissues after the infective bite, giving rise at intervals to the relapses so typical of this disease when transmitted by the mosquito. Since sporozoites are not present in schizogony, these tissue forms do not occur in malaria produced by the intravenous inoculation of blood from a malarial donor, and relapses do not occur. This proved phase of naturally transmitted malaria should probably tend to discourage further use of mosquitoes in induced therapeutic malaria in favor of intravenous inoculation from patient to patient in order that later relapses may be avoided.

Chalmers[192] observed 450 syphilitic patients treated with induced malaria and 99 patients with mosquito-inoculated malaria. Of the 450 patients whose malaria was induced by inoculation with blood, jaundice developed in 36. In half of these the jaundice occurred during the actual attack of malaria. In none of the 99 mosquito-inoculated patients did jaundice develop. Some of the attacks of hepatitis may have been caused by a specific icterogenic virus.

Kierland and McCreight[193] report on the utilization of chloroquine for the termination of malaria inoculata of the tertian type in 25 cases. The dosage was as follows: 1 Gm. followed in six hours by 0.5 Gm., 0.5 Gm. again in twenty-four hours and 0.5 Gm. again in forty-eight hours. The total dosage in 23 cases was 2.5 Gm. and in 2 cases 3.0 Gm. There was less likelihood of an additional paroxysm when the drug was given during defervescence. In 21 cases no febrile episodes occurred after administration of the drug was started, while in 4 an additional paroxysm occurred within twenty-four hours. In these 4 cases use of the drug had been started during a paroxysm while the temperature was ascending. Relapse did not occur during a two to eight months' observation period after treatment with chloroquine.

SYPHILIS AND OTHER DISEASES

Pinta.—Laboratory as well as clinical data of interest have been published during the past year. Dillon and Cooper[194] present the results of electrophoretic analyses of serums from 3 patients with pinta

191. Tissue Forms of the Malaria Parasite, editorial, Lancet **1**:182 (Jan. 31) 1948.

192. Chalmers, T. C., Jr.: The Occurrence of Jaundice in Therapeutic and Natural Malaria, J. Clin. Investigation **26**:1055 (Nov.) 1947.

193. Kierland, R. R., and McCreight, W. G.: The Termination of Therapeutic Malaria with Chloroquine, Am. J. Syph., Gonor. & Ven. Dis. **32**:57 (Jan.) 1948.

194. Dillon, M. L., and Cooper, G. R.: Electrophoretic Analysis of Serum from Patients with Pinta and Yaws, Am. J. Syph., Gonor. & Ven. Dis. **32**:251 (May) 1948.

and 3 with yaws. The pinta serums showed a slight increase in the content of gamma globulin, and the yaws serums showed a somewhat larger increase. The albumin was proportionately low in comparison with the gamma globulin content. No specific changes in the electrophoretic patterns indicative of the presence of unique proteins appeared in the diagrams of the pinta and yaws serums.

Blanco and deLaosa [195] provide a detailed description of the clinical and histopathologic appearance of experimentally produced pinta in man. Data are presented showing that in the majority of cases pinta is acquired in the first two decades of life. In experimental pinta, the period of incubation can be accurately established and varies from three to ten days, as a rule, sometimes being much longer. Adenopathy may accompany the primary lesion of pinta, and treponemes are usually demonstrable in material obtained from the puncture of nodes. These lymph nodes are small, hard, movable and painless. In 17 patients with experimental pinta and 39 with naturally acquired pinta, serologic tests for syphilis (flocculation and complement fixation tests) were performed serially, and in every case of primary pinta the reactions were negative, despite observation from forty days to more than two years. In the experimentally infected patients observed for a protracted period the reactions became positive after the appearance of secondary pinta.

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195. Blanco, F. L., and deLaosa, O.: The Primary Stage of Pinta, Am. J. Syph., Gonor. & Ven. Dis. **31**:600 (Nov.) 1947.

Book Reviews

Clinical Diagnosis by Laboratory Methods. By James C. Todd, M.D., and Arthur H. Sanford, M.D. Eleventh edition. Price, $7.50. Pp. 954, with 397 illustrations. Philadelphia: W. B. Saunders Company, 1948.

In this latest edition of a textbook on standard laboratory diagnosis of proved merit, the subject matter has been brought strictly up to date. Dr. Sanford has called on his associates in the Mayo Clinic to help in making new tests clear and clinically applicable to diagnosis of the disease states for which they were devised. The section on medical mycology has been expanded in keeping with the present widespread interest in this field. Modern methods for assay of penicillin and streptomycin in body fluids and of blood levels of the various vitamins are practically presented. Enough discussion of the various disease states is given to allow the reader to make a fairly accurate estimate of the importance of variations from normal with each test. It can truthfully be said that this is a worthy successor to long series of editions of a textbook which has always been among the leaders in the field of clinical diagnosis by laboratory methods.

Blood Pressure and Its Disorders, Including Angina Pectoris. By Johann Plesch, M.D. Second edition. Price, $6. Pp. 307, with 125 illustrations. Baltimore: The Williams & Wilkins Company, 1947.

This book is divided into three parts entitled "The Arterial Blood Pressure," "Venous Pressure" and "Angina Pectoris." The author, a former professor at the University of Berlin, expresses himself at times in sentences which are long and involved. The greater fault, however, is the presentation of unaccepted ideas which are without proof and seemingly conjectural. The first part contains a strong but unconvincing plea for the tonoscillograph. The second part contains concepts of renal function and its relation to venous pressure which are at variance with those presently accepted. The discussion of venous function and blood flow, however, is interesting and pertinent to the changing concept of the mechanism of congestive heart failure. The third part, which lends itself to practicality is, unfortunately, no improvement. Among measures advocated in the treatment of angina pectoris are the use of the Kosher diet, the ancient procedure of cupping and finally the author's own "auto urine treatment," wherein the patient's urine is injected intramuscularly. The latter treatment is recommended by the author for infectious hepatitis, mumps, whooping cough, asthma, hay fever, urticaria, meteorism and migraine. In summary it might be stated that the book has neither brevity nor clarity to recommend it.

Office Immunology. Edited by Dr. Marion B. Sulzberger and Dr. Rudolf L. Baer. Price, $6.50. Chicago: Year Book Publishers, Inc., 1947.

This is another of the general practice manuals and will join the others in the series happily. While it has been edited by Dr. Sulzberger and Dr. Baer, it has the collaborative aid of four other authors who are well known in the field of allergy, and all, if not directly associated with medical teaching, are experienced writers or investigators.

The contents of the volume are wisely arranged; there is ample space given to technic of an examination and to discussion of the diagnosis and treatment of the

common allergies which physicians in general practice encounter most frequently. There is an interesting chapter which describes the immunologic procedures useful in office practice for the prevention, diagnosis and treatment of the most important infectious diseases. Miscellaneous allergies about which less is known receive only briefest comment; gastrointestinal allergy, for example, receives but two and a half pages of space.

The editors state as their hope that their book may prove a useful textbook to the practicing physician. The ARCHIVES believes that it will fulfil this hope admirably.

History of Medicine. By Cecilia C. Mettler, Ed.B., A.M., Ph.D. Price, $8.50. Pp. 1215, with 16 illustrations. Philadelphia: The Blakiston Company, 1947.

In this volume approximately thirty-four hundred names are mentioned and at least an equal number of topics. The book thus attempts to be a comprehensive history of medicine, and, indeed, little of importance has been omitted.

The plan on which the work is built is sound: the history of anatomy and physiology, pharmacology, pathology and bacteriology is first dealt with. Physical diagnosis and how it developed as an art is next taken up. Then there follow chapters which candidates for specialty board examinations can read with benefit, for the history of medicine, neurology and psychiatry, dermatology and syphilis, pediatrics, surgery, obstetrics and gynecology, ophthalmology, otology and rhinolaryngology receives proper consideration. The development of each of these specialties is traced, from ancient times through the middle ages, the sixteenth century, the seventeenth century, the eighteenth century and up to fairly recent days in the nineteenth century.

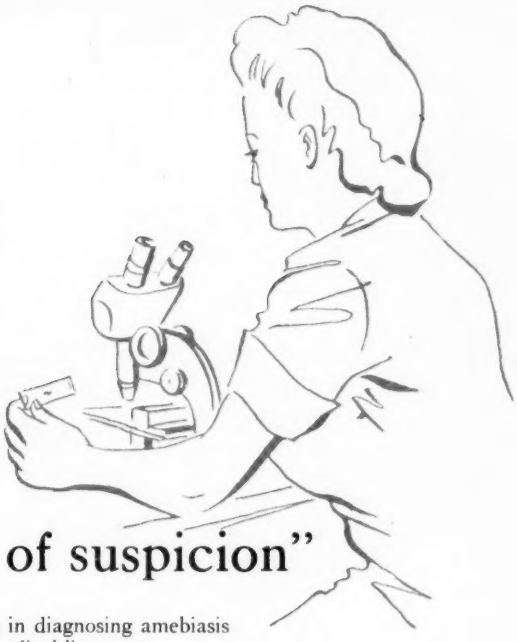
The trouble with the book—if there is any fault—lies in the fact that so much is attempted in a relatively small number of words. To be sure, there are twelve hundred and fifteen double-columned pages to peruse, but even so, as the author admits, only outstanding facts can be presented and these as briefly as possible. This makes reading not easy and takes away much of the color which can make medical history so fascinating.

On the other hand, it is the kind of a work which should prove particularly valuable for reference. Besides the names and the topics already mentioned, at the end of each chapter is listed a bibliography of selected readings which is chosen carefully, and the footnotes at the bottom of nearly every page guide an inquisitive reader to hosts of attractive original sources.

On the whole, the author deserves heartiest congratulations for having accomplished such an arduous task as the preparation of this book must have entailed. Anyone interested in medical history will be grateful for it.

A Symposium on the Use of Isotopes in Biology and Medicine. By Hans T. Clarke, and others. Price, $5. Pp. 445. Madison, Wis.: University of Wisconsin Press, 1948.

The twenty odd articles by various experts in the field of biophysics here assembled pretty well cover the subject from the standpoint of the general physician. Theoretic considerations are followed by discussions of the practical applications of isotope technic in research and in practice. There are good bibliographies after each chapter.



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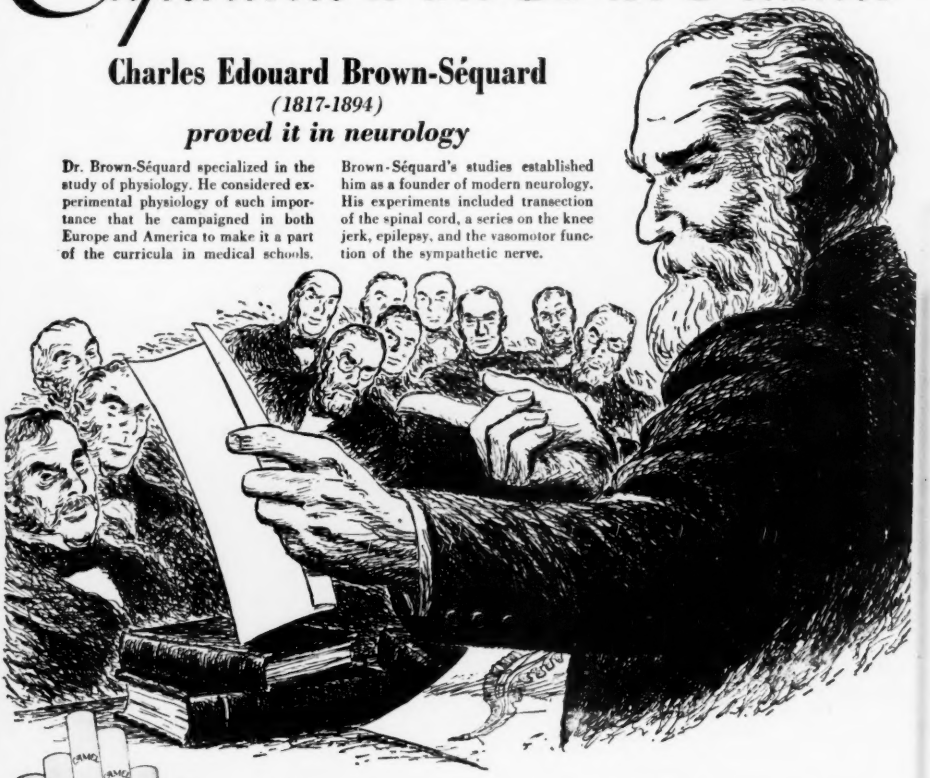

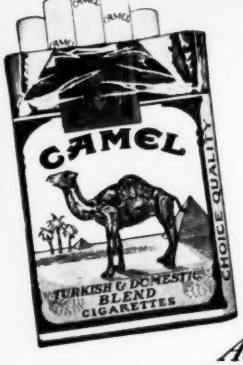

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